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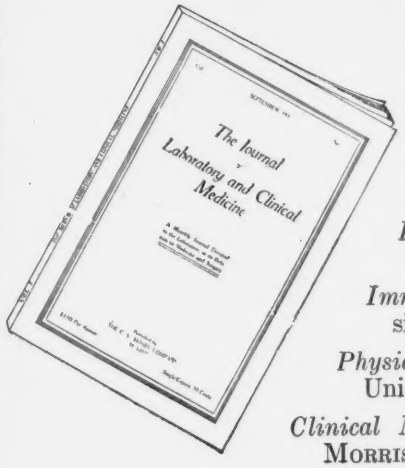


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# THE EFFECT OF PULMONARY TUBERCULOSIS ON RENAL FUNCTION[1]

CHARLES W. MILLS AND JOHN T. HENDERSON

*From the Laboratory of the Loomis Sanatorium, Loomis, New York*

The experiments reported in this paper were undertaken with a view to determining, by the use of some of the recently devised tests for kidney function, whether and to what extent the presence of pulmonary tuberculosis impairs kidney function.

Autopsies on subjects dying of pulmonary tuberculosis frequently disclose pathological changes in the kidneys. Walsh (1) (2) in a series of 100 cases found the most common changes to be an acute parenchymatous nephritis (36 per cent) and a chronic parenchymatous nephritis (38 per cent). Other less common lesions were interstitial nephritis (14 per cent), diffuse nephritis (4 per cent), amyloid degeneration (5 per cent), cloudy swelling (7 per cent), passive congestion (1 per cent). He also found tubercles in the kidneys in 55 per cent of his cases. Funk (3) in a recent report has confirmed these results as to nephritis, his percentages being very similar to Walsh's. It is probable that many of these changes occur very late in the disease or are terminal.

As a rule there are no symptoms of nephritis even at the end. Blood pressure is usually below normal, there is no cardiac enlargement, and no very evident changes in the amount or frequency of the urine. Edema not infrequently occurs as a terminal event, but this is as easily attributable to myocardial weakness as to nephritis.

The presence in the urine of small amounts of albumin and sometimes casts during the course of the disease is not at all uncommon, and has been noted by most observers who have made careful routine examinations. By our using delicate methods as high as 40 per cent of our sanatorium cases at some time during their stay have shown traces of albumin, with or without hyaline casts. A few cases will show albumin or casts in larger amounts. Fever influences these findings somewhat,

[1] We take pleasure here in acknowledging our indebtedness to Dr. Leonard G. Rowntree for helpful suggestions at the inception of this study, and especially to Dr. Herman O. Mosenthal for most valuable criticisms of our results.

but they cannot be referred entirely to this cause, as albumin is often found also in afebrile cases. When in these minimal amounts we have not been able to determine that it has any serious significance. As the pulmonary condition improves the trace of albumin often disappears, although this is by no means always the case.

In view of these autopsy, clinical and urinary findings it seemed to offer to us an interesting study to see if, in the ordinary course of pulmonary tuberculosis, there is sufficient damage to the kidney, either from nephritis or tubercle formation, to cause a disturbance of renal function such as may be revealed by modern functional tests. Funk (3) has recently reported a series of cases in which he tested the renal function by phenolsulphonephthalein. His conclusion is that renal function in pulmonary tuberculosis is good and is impaired only when there is evidence of structural damage to the kidney. He found that in the last few days of life there may be a moderately lowered phthalein excretion.

## SERIES I. EXCRETION AND RETENTION TESTS

Our first experiments were with Rowntree and Geraghty's (4) (5) phenolsulphonephthalein test, with the lactose excretion test of Schlayer (6), with Marshall's (7) test for blood urea, and with Ambard's (8) (9) (10) coefficient of urea excretion. A series of 44 cases was tested; the phthalein test in 43, blood urea in 42, lactose in 19, and Ambard's in 32. Most of the cases were selected from far advanced pulmonary patients with an unfavorable prognosis. Twenty-nine of the cases showed albumin or casts in the urine, only a trace in 19 of these, and larger amounts in 10. We did not however, except in two cases (series 1, no. 8 and no. 1), make tests in the last few days of life, which probably explains the slight difference between our results and Funk's.

The phthalein test was made according to Rowntree and Geraghty's technique (4). An excretion of 60 per cent or more in two hours was considered normal.

Lactose was given according to Schlayer's technique (6) (15). Urine specimens obtained later than six hours after the administration of the drug, showing a positive sugar test, were regarded as abnormal.

Blood urea was determined according to Marshall's method (7) (15). There appears to be considerable confusion as to what should be regarded as the upper limit of normal. Various authors give all the way from 25 mgm. per 100 cc. up to 55 mgm. Mosenthal and Lewis (10),

after a review of the literature on the subject, select 30 mgm. per 100 cc. as the upper normal limit and believe that amounts above this, while not necessarily abnormal, should receive very careful investigation. On the other hand Rowntree, Geraghty and Marshall (15) adopt 55 mgm. as the upper normal limit. Diet evidently may play an important part. As no attempt was made in our cases to control the diet we have not considered 4 cases in our series, with amounts of a few milligrams above 30, but without any other evidence of functional abnormality, as being abnormal. Ambard (8) (10) maintains that the actual amount of urea in the blood is less important than the rate at which the kidneys are able to excrete it, and attempts to express this by a coefficient determined by means of a formula between the blood urea and the urea in the urine of the same day. The coefficient thus obtained is normally not higher than 0.09. The formula is too long to be given here but can be found in the articles referred to. The urea in the urine was determined by Marshall's method (11).

*Discussion of results in series I.* By none of these tests could it be found that pulmonary tuberculosis has any serious effect on kidney function. All of our cases, even when far advanced, febrile and unfavorable, and with albumin and casts in the urine were normal except ten cases. In most of these the abnormality was only slight. These ten cases are shown in table 1.

Cases 1, 2, 3, and 4 show definite clinical evidence of renal or cardio-renal disease. All of these cases were favorable so far as the pulmonary condition was concerned, and the tuberculosis did not appear to have been an etiological factor in the nephritis. Cases 1 and 2 show a lowered phthalein excretion and an increased blood urea; case 3, lowered phthalein, and case 4, only an increase in blood urea.

Cases 5, 6, and 7 are cases of renal tuberculosis, cases 6 and 7 definitely diagnosed by cytoscopic examination, and case 5 suspected from history and symptoms. These cases show only slight abnormality: in cases 5 and 6 there is a slightly lowered phthalein excretion and in case 7 a slightly high Ambard.

Case 8 was a boy dying of tuberculous meningitis, complicating a far advanced pulmonary tuberculosis. No urine was obtained at the end of the second hour, but a phthalein of 40 per cent for the first hour would indicate little if any deficiency in phthalein excretion. The blood urea is slightly high.

TABLE 1

| GENERAL DATA | | | | | URINALYSIS | | | | FUNCTIONAL TESTS | | | | | | | | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number | Name, sex, age | Clinical condition | Duration of tuberculosis | Blood pressure | Amount | Specific gravity | Albumin | Microscopical | Date | Phthalein | | | Lactose | Blood urea, mgm. in 100 cc. | Ambard's | | |
| | | | | | | | | | | First hour | Second hour | Total | | | | | |
| | | | | | | | | | | *per cent* | *per cent* | *per cent* | | | | | |
| 1 | N. B. M., 50 | M. A. Febrile, uraemic coma | Three years | 200 | Single specimen | | + | Few hyaline casts, red blood cells and white blood cells | December 26, 1914 | 24 | 1 | 25 | | 60.0 | | | Died, December 27, 1914 |
| 2 | T. N. M., 58 | F. A. Afebrile, chronic nephritis | Twenty-nine years | 168<br>98 | 1200 | 1016 | Trace | Few hyaline casts, red blood cells, many white blood cells | February 2, 1915 | 30 | 16 | 46 | | 76.9 | | | Died, February 24, 1915 |
| 3 | J. L. M., 45 | F. A. Afebrile, diabetes mellitus, chronic nephritis | Six months | 165<br>100 | 1300 | 1027 | + | Few hyaline casts, white blood cells | February 4, 1915 | 22 | 25 | 47 | | 33.8 | 0.07 | | Died, April 13, 1916 |
| 4 | T. W. M., 53 | F. A. Afebrile, chronic nephritis | Nineteen years | 190<br>110 | 2300 | 1012 | + | Hyaline and granular casts, few red blood cells and white blood cells | September 14, 1915 | 42 | 24 | 66 | 4 hrs. | 42.9 | | | |
| 5 | W. J. M., 20 | Tuberculosis of the hip, (healed) tuberculous orchitis, orchidectomy one year ago | Eleven years | 140<br>95 | 1050 | 1020 | + | Many pus cells | January 21, 1915 | 34 | 20 | 54 | | 29.0 | | | See table 2, case 9 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 | W.C. M., 33 | F. A. Afebrile, bilateral renal tuberculosis | Eight years | 135 90 | 1700 | 1017 | + | Few hyaline and granular casts. Many white blood cells. Few tubercle bacilli | January 29, 1915 | 37 | 18 | 55 | 4 hrs. | 27.0 | 0.05 | See table 2, case 7, died May 5, 1916 |
| 7 | M.B. F., 36 | Bilateral renal tuberculosis | Five years | 125 90 | 1640 | 1009 | + | Many white blood cells, many tubercle bacilli | March 3, 1915 | 70 | 18 | 88 | | 29.0 | 1.2 | See table 2, case 8 |
| 8 | E. R. M., 20 | F. A. Febrile, tuberculous laryngitis and meningitis | Three years | 105 65 | 1850 | 1012 | 0 | Few white blood cells | February 22, 1915 | 40 | | | | 42.9 | | Died, February 24, 1915 |
| 9 | E. B. F., 43 | M. A. Afebrile, favorable | Sixteen years | 120 80 | 1900 | 1020 | 0 | Few white blood cells | March 11, 1915 | 65 | 5 | 70 | 10 hrs. | 35.0 | 0.09 | |
| 10 | G. G. M., 36 | F. A. Febrile, unfavorable | Twelve years | 130 98 | Single specimen | 1013 | Faint trace | Many white blood cells | March 18, 1915 | 60 | 21 | 81 | | 44.4 | 0.1 | |

M. A. Moderately advanced.
F. A. Far advanced.

Case 9 was a nurse in excellent pulmonary condition. No clinical abnormality could be found to account for the delayed lactose excretion. She was of a very neurotic temperament and was greatly upset nervously at having the tests performed, but it seems very doubtful that this could have influenced the lactose excretion.

Case 10 was a far advanced unfavorable pulmonary tuberculosis. The only functional abnormalities were a slightly high blood urea and Ambard's coefficient.

*Conclusions from series 1.* From this first series of 44 cases therefore we must conclude that pulmonary tuberculosis, even when far advanced and unfavorable, is not accompanied by any disturbance of renal function of sufficient grade to be detected by the excretion and retention tests employed. Only when the pulmonary disease is complicated by clinically determinable renal disease (chronic nephritis and renal tuberculosis in our cases) is renal function disturbed.

### SERIES 2. MOSENTHAL'S TEST MEAL

While making this first series of tests our attention was called to the work being done by Mosenthal in Dr. Janeway's clinic at the Johns Hopkins Hospital, with a modification of the Hedinger and Schlayer method, and we decided to try a second series of cases with this method.

Hedinger and Schlayer's method (12) briefly stated is as follows: The subject is given a measured diet containing definite quantities of fluid, nitrogen and sodium chloride. The normal rate at which these substances should be excreted by the kidneys having been determined, the abnormal variations in secretion which occur in various diseases can be shown. These results can easily be plotted in the form of curves or diagrams and, with the normal curve for comparison, any variations noted. Mosenthal (13) (10) has modified this method in the direction of simplicity and practicability. For a full description of these methods and for the theories which underlie their use the original articles should be consulted.

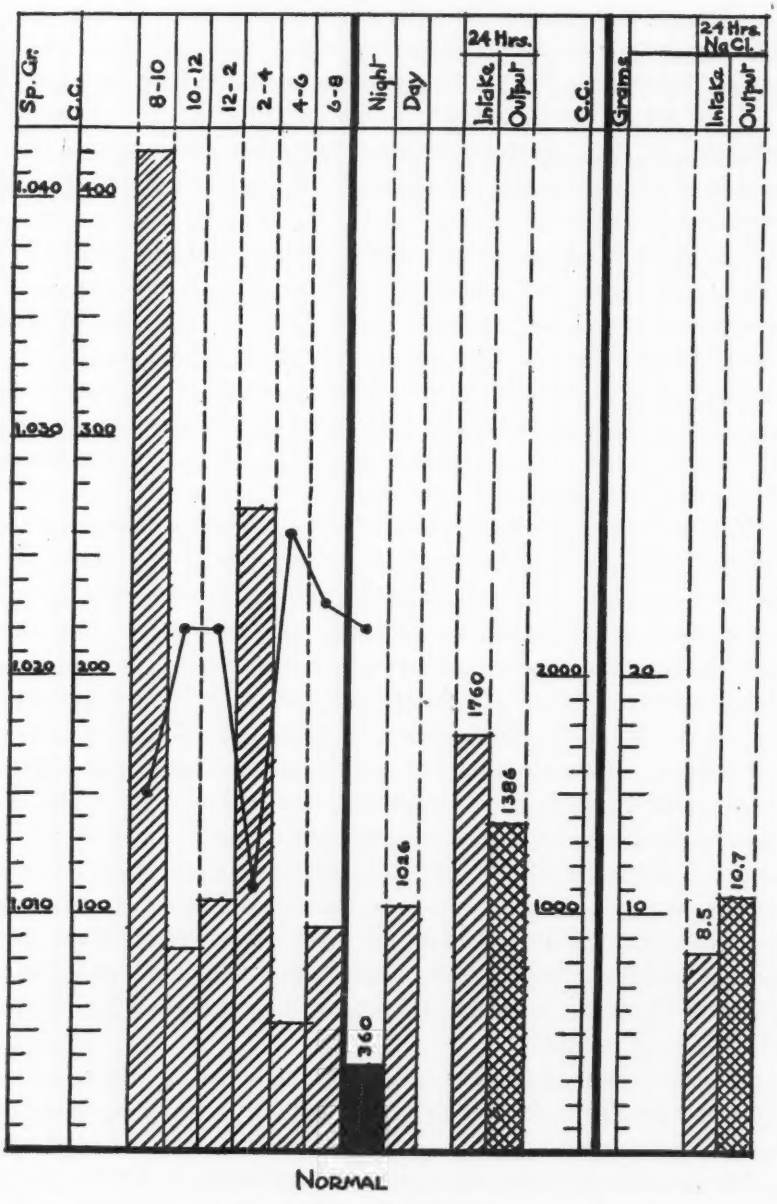
We have tested a series of 43 cases by this method. The patients were given the three meal diet used by Mosenthal (13) containing approximately 1760 cc. of fluid, 8.5 grams of sodium chloride and 13.4 grams of nitrogen. The urine was collected at two hour intervals from 8 a.m. to 8 p.m. and the total night urine from 8 p.m. to 8 a.m. On each of these specimens a determination of the amount (water secretion) and of the specific gravity was made. The sodium chloride in

the total day and night specimens was estimated by Volhard's method (14). We did not attempt to make nitrogen determinations.

The results obtained were then plotted in the accompanying diagrams. The water secretion for each two hour specimen is represented by the columns, and the specific gravity by the line. A comparison of the day and night output and of the total intake and output of fluid is shown in the center of the charts, and to the extreme right, the intake and output of sodium chloride.

According to Mosenthal's investigation the normal curve should show the following characteristics: the night urine should not be more than 400 cc. in amount, the specific gravity of the night urine should be 1018 or over, and there should be a variation of at least nine points between the highest and lowest specific gravity. In normal cases also the water curve should show wide fluctuations between the different specimens. All of these characteristics are well shown in the accompanying chart of a normal case (diagram I, case 15). Hedinger and Schlayer (12) lay considerable stress on a diminution of the sodium chloride and nitrogen excretion. Mosenthal however takes exception to this and believes that there are so many external factors which may influence the excretion of these substances on the particular day of the test, that only a markedly diminished excretion should be considered definitely abnormal. In estimating results in this present series it makes considerable difference whether we follow Hedinger and Schlayer's or Mosenthal's criteria. If we regard a moderate degree of salt retention as indicating a disturbance of renal function then a great number of our cases which would otherwise be normal must be regarded as showing a deficient kidney function. We have not had an opportunity of checking up our results on this point by a series of non-tuberculous normal cases. This however Mosenthal has done, and as his work is more recent than that of Hedinger and Schlayer and as we have followed the details of his method instead of those of the latter authors, we have adopted his criteria in estimating our results.

Our supper hour, 5.30, was a half hour later than Mosenthal's and this would tend to make the night urine slightly greater in amount and lower in specific gravity. We have not therefore regarded as abnormal the few cases in our series which show a night urine of 400 to 450 cc. or a night specific gravity of 1017. In all other points we have followed exactly Mosenthal's method.




EXPLANATION OF DIAGRAMS:

Water secretion is represented by the columns, specific gravity by the line. Comparison of day and night output and of total intake and output is shown in center. The intake and output of sodium chloride are presented at the extreme right.

The cases for this second series were selected from the same type of patients as in the first series; that is, for the most part from far advanced unfavorable pulmonary cases with traces of albumin or casts in the urine. A few of the patients in series 1 who were still in the sanatorium were included in this second series. The few cases in the sanatorium who showed clinical evidence of nephritis or renal tuberculosis were also included.

The results of these tests are shown in table 2.

*Discussion of results in series 2.* In analyzing the results in this series we may group the cases in varying ways. In the table they have been analyzed according to their renal condition as determined by ordinary clinical tests and will be discussed first on this basis. They fall into the following groups:

Cases 1 to 4. Hypertensive nephritis complicating pulmonary tuberculosis.

Cases 5 to 6. Terminal edema.

Cases 7 to 11. Genito-urinary tuberculosis.

Cases 12 to 18. Albumin and casts.

Cases 19 to 38. Trace of albumin, or few hyaline casts.

Cases 39 to 43. Normal.

The results of the functional tests may be divided for convenience into three groups according to the degree of functional disturbance as, first, normal; second, slight functional disturbance, that is to say, a night urine of 450 to 600 cc., or a night specific gravity a few points below 1017, or a variation of specific gravity of only 6 or 8 points; third, more marked functional disturbance, that is, with the above abnormalities more pronounced and in combination, and also the cases with a marked deficiency in sodium chloride excretion. This grouping is of course arbitrary and somewhat rough, but we believe that it is exact enough for the purpose of this analysis.

Table 3 shows how the cases fall in this grouping.

The most striking fact in looking at this table is that the cases of marked disturbance of function are all, except three, cases which have definite clinical evidence, aside from albumin and casts, of renal disease. Where albumin and casts were the only renal abnormality two-thirds of the functional tests were normal and the other third, except for three cases, showed only slight departure from normal. In a test of this character it is necessarily difficult to draw a hard and fast line between

TABLE 2

| GENERAL DATA | | | | | URINALYSIS | | | | | FUNCTIONAL TEST | | | | | | | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number | Name, sex, age | Clinical condition | Duration | Blood pressure | Albumin | Hyaline casts | Granular casts | Red blood cells | Pus | Date | Amount | | Specific gravity | | | Sodium chloride, grams | |
| | | | | | | | | | | | Day | Night | High | Low | Night | | |
| 1 | E. W. S.<br>F. 63 | F. A. Afebrile, favorable | Fourteen years | 175<br>85 | Trace | Few | | | | September 10, 1915 | 1225 | 930 | 18 | 9 | 13 | 9.0 | Phthalein 70 per cent |
| 2 | L. A. E.<br>F. 67 | F. A. Afebrile, cardiac hypertrophy and dyspnoea | Twelve years | 170<br>115 | Trace | Few | | Few | + | August 19, 1915 | 680 | 560 | 14 | 7 | 14 | 5.5 | Died, February 24, 1916 |
| 3 | T. W. W.<br>M. 53 | F. A. Afebrile, Recent headaches | Nineteen years | 190<br>110 | ++ | + | + | Few | | September 10, 1915 | 755 | 750 | 15 | 11 | 14 | 7.2 | Phthalein 66 per cent. Blood urea 42.9 mgm. in 100 cc. Lactose 4 hours |
| 4 | J. P. M.<br>M. 52 | M. A. Afebrile, slight arteriosclerosis | One year | 160<br>98 | 0 | Few | 0 | | | November 4, 1916 | 1830 | 560 | 18 | 8 | 16 | 10.3 | |
| 5 | E. H.<br>F. 27 | F. A. Active febrile, unfavorable, terminal edema | Three years | 85<br>60 | + | + | + | Few | + | December 23, 1915 | 264 | 330 | 25 | 16 | 16 | 1.1 | Phthalein 60 per cent. See case 14, died February 8, 1916 |
| 6 | M. E. M.<br>F. 24 | F. A. Febrile, unfavorable, terminal edema | Four years | 105<br>80 | ++ | + | + | Few | + | June 12, 1916 | 410 | 360 | 22 | 15 | 18 | 0.9 | Died, August 25, 1916 |
| 7 | W. H. C.<br>M. 33 | F. A. Afebrile, renal tuberculosis. | Eight years (Renal, two years) | 135<br>90 | + | + | 0 | | ++ | July 10, 1915 | 820 | 605 | 18 | 16 | 18 | 11.4 | Phthalein 55 per cent. Blood urea 27 mgm. in 100 cc. Lactose 4 hours, died, May 6, 1916. |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | M. D. B. F. 36 | Renal tuberculosis. Afebrile | Five years | 125 90 | + | 0 | 0 | Few | ++ | September 2, 1915 | 1105 | 635 | 13 | 9 | 13 | 10.3 | Phthalein 88 per cent. Blood urea 29 mgm. in 100 cc. |
| 9 | W. J. M. 20 | Tuberculous orchitis, afebrile | Eighteen months | 140 95 | + | 0 | 0 | | + | July 16, 1915 | 535 | 335 | 22 | 18 | 21 | 6.4 | Phthalein 54 per cent. Blood urea 29 mgm. in 100 cc. |
| 10 | F. T. H. M. 40 | F. A. Febrile, unfavorable, tuberculous orchitis | Two years | 125 80 | + | Few | 0 | Few | + | July 30, 1915 | 1100 | 400 | 15 | 10 | 15 | 7.2 | Phthalein 73 per cent. Blood urea 19 mgm. in 100 cc. |
| 11 | F. B. O. M. 37 | F. A. Afebrile, tuberculous orchitis | Seven years | 88 60 | + | Few | 0 | Few | + | September 17, 1915 | 1580 | 780 | 16 | 7 | 11 | 10.3 | Died, May 6, 1917 |
| 12 | M. E. G. F. 30 | Incipient. Afebrile, favorable | One year | 130 90 | + | + | + | Few | + | September 26, 1915 | 1245 | 440 | 19 | 7 | 14 | 5.7 | |
| 13 | M. S. R. M. 26 | F. A. Unfavorable, febrile | Six years | 115 80 | Trace | + | + | | | September 25, 1915 | 700 | 600 | 20 | 8 | 17 | 5.5 | |
| 14 | E. H. F. 27 | F. A. Febrile | Three years | 85 60 | + | + | + | | + | September 23, 1915 | 525 | 530 | 30 | 5 | 15 | 4.4 | See case 5, died, February 8, 1916 |
| 15 | M. L. M. 20 | F. A. Afebrile, favorable | One year | 130 90 | + | + | 0 | Few | | October 13, 1915 | 1026 | 360 | 28 | 11 | 22 | 11.7 | Lactose 6 hours |
| 16 | H. C. E. M. 38 | F. A. Afebrile, unfavorable | Eight years | | + | Few | 0 | | + | October 1, 1915 | 1330 | Lost | 22 | 11 | ? | ? | |
| 17 | M. J. D. F. 26 | F. A. Afebrile, unfavorable | Three years | 110 75 | + | + | + | Few | + | September 4, 1915 | 505 | 320 | 22 | 8 | 16 | 6 | |
| 18 | W. G. M. 24 | F. A. Febrile, unfavorable | Four years | | + | Few | 0 | | | September 4, 1915 | 445 | 230 | 28 | 12 | 28 | 3.5 | |
| 19 | E. E. Y. F. 35 | F. A. Afebrile, unfavorable | One year | 132 86 | Trace | 0 | 0 | | + | September 26, 1915 | 1830 | 560 | 18 | 8 | 16 | 10.3 | Died, July 31, 1916 |
| 20 | W. R. S. M. 28 | F. A. Febrile, unfavorable | Six years | 110 85 | Trace | 0 | 0 | | | October 2, 1915 | 1185 | 390 | 17 | 5 | 11 | 6.3 | Died, February 19, 1916 |
| 21 | W. B. C. M. 38 | F. A. Febrile, unfavorable | One year | 120 60 | Trace | Few | 0 | | | July 14, 1915 | 620 | 385 | 21 | 10 | 10 | 4.3 | Phthalein 73 per cent. Blood urea 30 mgm. in 100 cc. Died, November 14, 1915 |

TABLE 2—*Continued*

| GENERAL DATA | | | | | URINALYSIS | | | | | FUNCTIONAL TEST | | | | | | | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number | Name, sex, age | Clinical condition | Duration | Blood pressure | Albumin | Hyaline casts | Granular casts | Red blood cells | Pus | Date | Amount | | Specific gravity | | | Sodium chloride, grams | |
| | | | | | | | | | | | Day | Night | High | Low | Night | | |
| 22 | E. R. F. 47 | M. A. Afebrile, favorable | One year | 158 90 | Trace | 0 | 0 | | | October 1, 1915 | 1420 | 300 | 20 | 8 | 20 | 8.4 | |
| 23 | W. M. B. F. 33 | F. A. Afebrile, favorable | Four years | 100 75 | Trace | 0 | 0 | | | September 26, 1915 | 1235 | 130 | 25 | 7 | 25 | 5.0 | |
| 24 | A. R. M. 30 | M. A. Afebrile, favorable | Two years | 120 60 | Trace | Few | 0 | | | September 25, 1915 | 1560 | 350 | 19 | 11 | 19 | 8.6 | |
| 25 | E. S. V. F. 29 | F. A. Afebrile, unfavorable | Eight years | 100 75 | Trace | 0 | 0 | | | September 11, 1915 | 855 | 350 | 18 | 5 | 2 | 4.9 | Died, April 7, 1916 |
| 26 | R. A. G. M. 22 | F. A. Afebrile, unfavorable | Two years | 115 60 | Trace | Few | 0 | | | September 17, 1915 | 900 | 400 | 27 | 8 | 17 | 4.1 | |
| 27 | J. S. B. M. 22 | M. A. Afebrile, favorable | Seven months | 136 90 | Trace | 0 | 0 | | | September 25, 1915 | 1130 | 330 | 19 | 8 | 19 | 5.9 | |
| 28 | R. H. A. F. 22 | F. A. Afebrile, favorable | Seven years | 106 80 | 0 | Few | 0 | | | September 24, 1915 | 1500 | 215 | 22 | 8 | 22 | 6.4 | |
| 29 | A. V. H. M. 20 | F. A. Afebrile, unfavorable | Three years | 145 75 | Trace | Few | 0 | | | September 5, 1915 | 1190 | 270 | 22 | 8 | 22 | 7.7 | |
| 30 | C. S. C. F. 35 | F. A. Febrile, unfavorable | Ten years | 110 70 | Trace | Few | 0 | | | October 2, 1915 | 1060 | 360 | 17 | 7 | 17 | 3.5 | Died, April 26, 1916 |
| 31 | H. B. R. M. 27 | F. A. Febrile, unfavorable | Six years | 100 70 | Trace | 0 | 0 | | | August 3, 1915 | 865 | 250 | 20 | 10 | 20 | 6.9 | Phthalein 72 per cent. Died, July 8, 1916 |
| 32 | R. A. W. F. 27 | F. A. Febrile, unfavorable | Four years | 122 90 | Trace | Few | Few | | | August 31, 1915 | 1120 | 300 | 19 | 8 | 18 | 5.0 | Died, July 12, 1916 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 33 | C. F. R. M., 21 | F. A. Febrile, unfavorable | Five years | 115 80 | Trace | Few | 0 | Few | + | July 30, 1915 | 1000 | 360 | 18 | 8 | 18 | 7.6 | Phthalein 70 per cent. Blood urea 17 mgm. in 100 cc. Lactose 4 hrs. Died, January 2, 1917 |
| 34 | M. K. K. F. 21 | F. A. Febrile, unfavorable | One year | | 0 | Few | 0 | Few | | August 31, 1915 | 480 | 270 | 24 | 15 | 24 | 3.8 | Died, April 17, 1916 |
| 35 | A. S. F. 40 | F. A. Febrile, unfavorable | Four years | 110 82 | Trace | 0 | 0 | | | September 9, 1915 | 795 | 390 | 21 | 7 | 10 | 3.3 | |
| 36 | J. W. S. M. 47 | F. A. Afebrile, unfavorable | Three years | 100 65 | Trace | 0 | 0 | | | September 10, 1915 | 485 | 1000 | 22 | 8 | 8 | 5.0 | |
| 37 | H. E. M. M. 21 | F. A. Febrile, unfavorable | Fifteen months | | Trace | Few | Few | | | September 17, 1915 | 905 | 960 | 14 | 11 | 14 | 6.0 | Died, May 2, 1916 |
| 38 | J. V. C. M. 46 | F. A. Febrile, unfavorable | Twenty-five years | | Trace | 0 | Few | | | September 9, 1915 | 750 | 710 | 17 | 12 | ? | 6.4 | Died, March 18, 1916 |
| 39 | M. J. F. 35 | M. A. Afebrile, favorable | Fourteen years | 120 75 | 0 | 0 | 0 | | | July 23, 1915 | 880 | 430 | 18 | 7 | 15 | 5.3 | Phthalein 72 per cent. Blood urea, 36 mgm. in 100 cc. |
| 40 | W. K. F. 38 | F. A. Afebrile, unfavorable | Three years | 125 85 | 0 | 0 | 0 | | | September 15, 1915 | 1253 | 250 | 17 | 5 | 15 | 5.1 | |
| 41 | J. P. O. M. 18 | F. A. Afebrile, favorable | Six years | 115 55 | 0 | 0 | 0 | | | July 23, 1915 | 1505 | 420 | 21 | 8 | 19 | 9.7 | Phthalein 80 per cent. Blood urea 22 mgm. in 100 cc. |
| 42 | J. T. H. M. 26 | M. A. Afebrile, favorable | Three years | 125 75 | 0 | 0 | 0 | | | July 10, 1915 | 570 | 435 | 25 | 17 | 24 | 5.6 | Phthalein 61 per cent. Blood urea 34 mgm. in 100 cc. |
| 43 | A. G. M. 21 | F. A. Febrile, unfavorable | Three years | 120 65 | 0 | 0 | 0 | | | September 24, 1915 | 625 | 270 | 26 | 17 | 22 | 4.8 | Phthalein 78 per cent. Blood urea 24 mgm. in 100 cc. Lactose 4 hours |

the normal and the abnormal limits, and we feel that these slight abnormalities found in many of the cases should not be regarded too seriously.

Let us consider these various groups a little more in detail. Group 1 shows a definite functional picture which Mosenthal (13) has described in hypertensive nephritis of the chronic interstitial or arteriosclerotic type. The night urine is increased and of a lowered specific gravity, and in two of the cases there is a tendency to fixation of the specific gravity curve. Diagram II, graphically illustrating case 3, shows these changes.

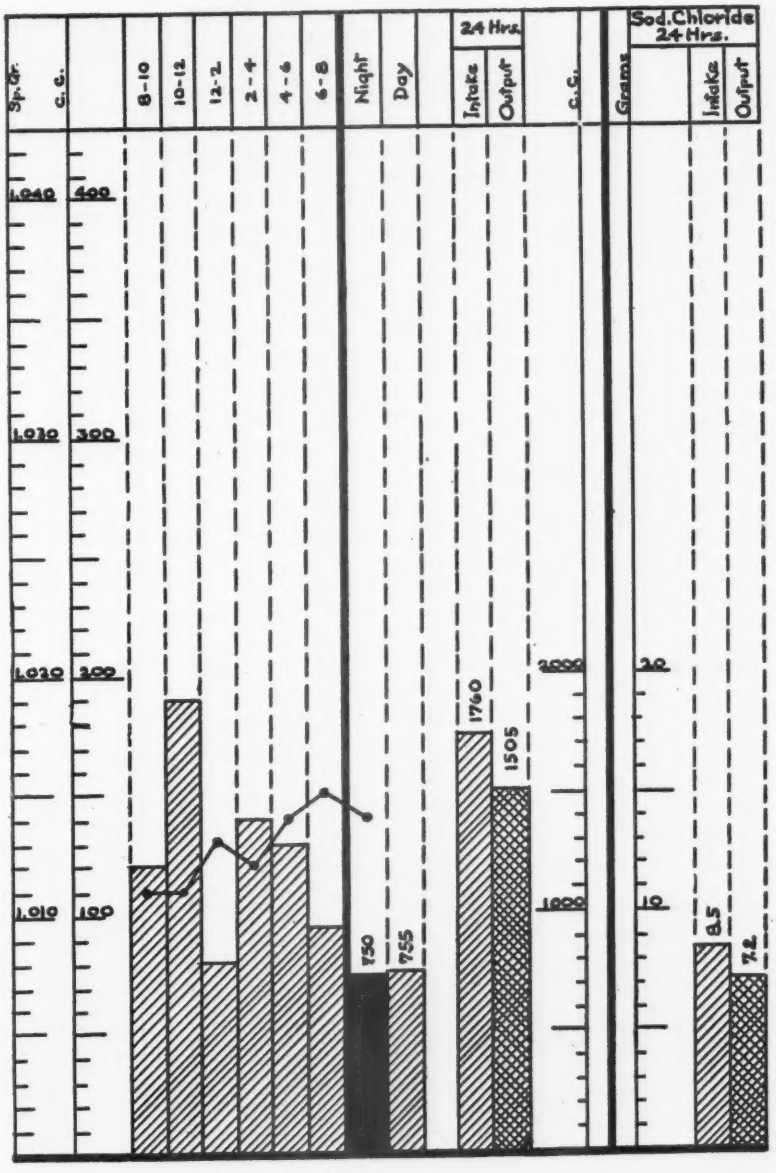
Group 2 we have described as terminal edema. Not infrequently in the course of pulmonary tuberculosis an edema, general or localized, occurs from a few days to a few weeks before death. It is a sign of

TABLE 3

| GROUP | CLINICAL CONDITION | FUNCTIONAL TEST | | | |
|---|---|---|---|---|---|
| | | Normal | Slight | Marked | Total |
| 1 | Chronic nephritis | | 1 | 3 | 4 |
| 2 | Terminal edema | | | 2 | 2 |
| 3 | Genito-urinary tuberculosis | | | 5 | 5 |
| 4 | Albumin and casts | 3 | 4 | | 7 |
| 5 | Trace of albumin and hyaline casts | 13 | 4 | 3 | 20 |
| 6 | Normal | 3 | 2 | | 5 |
| Total | | 19 | 11 | 13 | 43 |

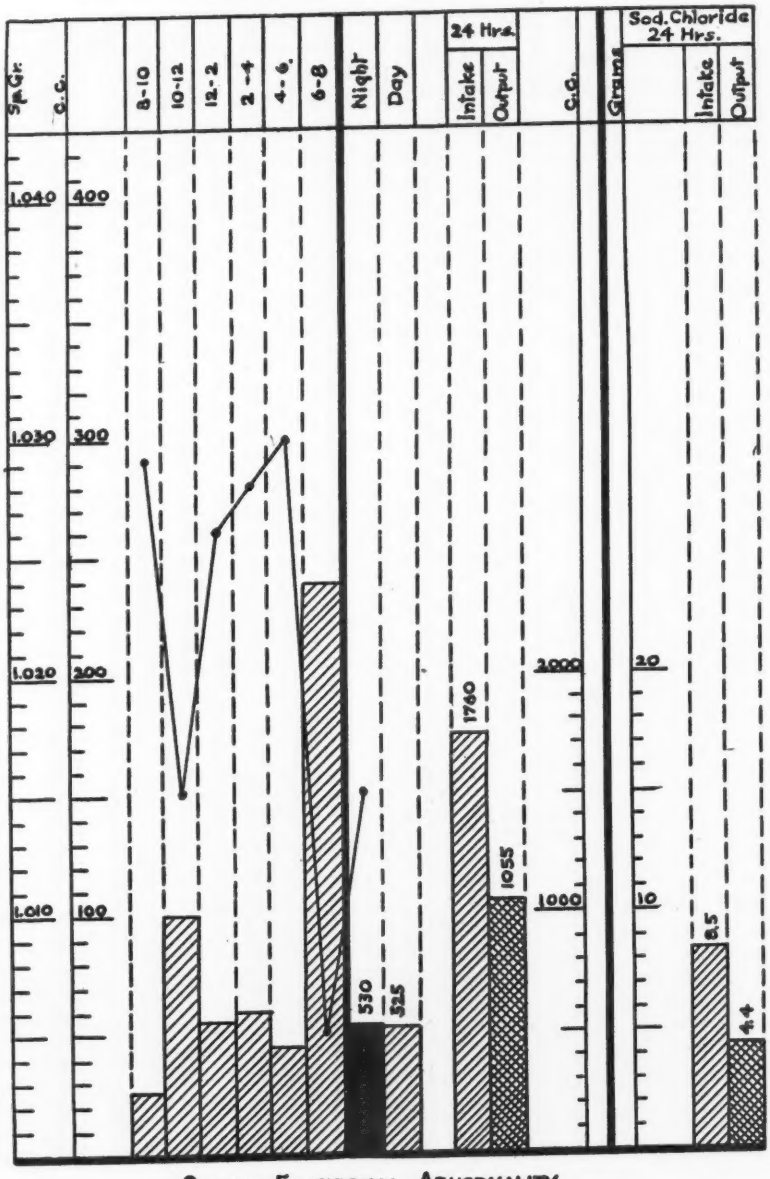
most grave prognostic significance, but whether it depends primarily on a parenchymatous nephritis or myocardial weakness, the weakened right ventricle being unable to efficiently keep up the circulation through the greatly reduced pulmonary vessels, we have never been able to determine. Probably both factors play a part. Parenchymatous changes are usually found in these kidneys at autopsy, but on the other hand the blood pressure is as a rule very low. The heart sounds may be weak, but murmurs are rare. We have never seen much response to any kind of therapy. Digitalis does no good and salt-free diet has not removed the edema in the few cases in which we have tried it. The picture obtained from the functional test in these two cases is a very definite one but does not help any in determining the etiology of the condition, as, according to Mosenthal (13), this same picture is given both by cases of parenchymatous nephritis and by broken cardiac compensation. The characteristic picture is a reduction of water and espe-

DIAGRAM II — CASE 3.



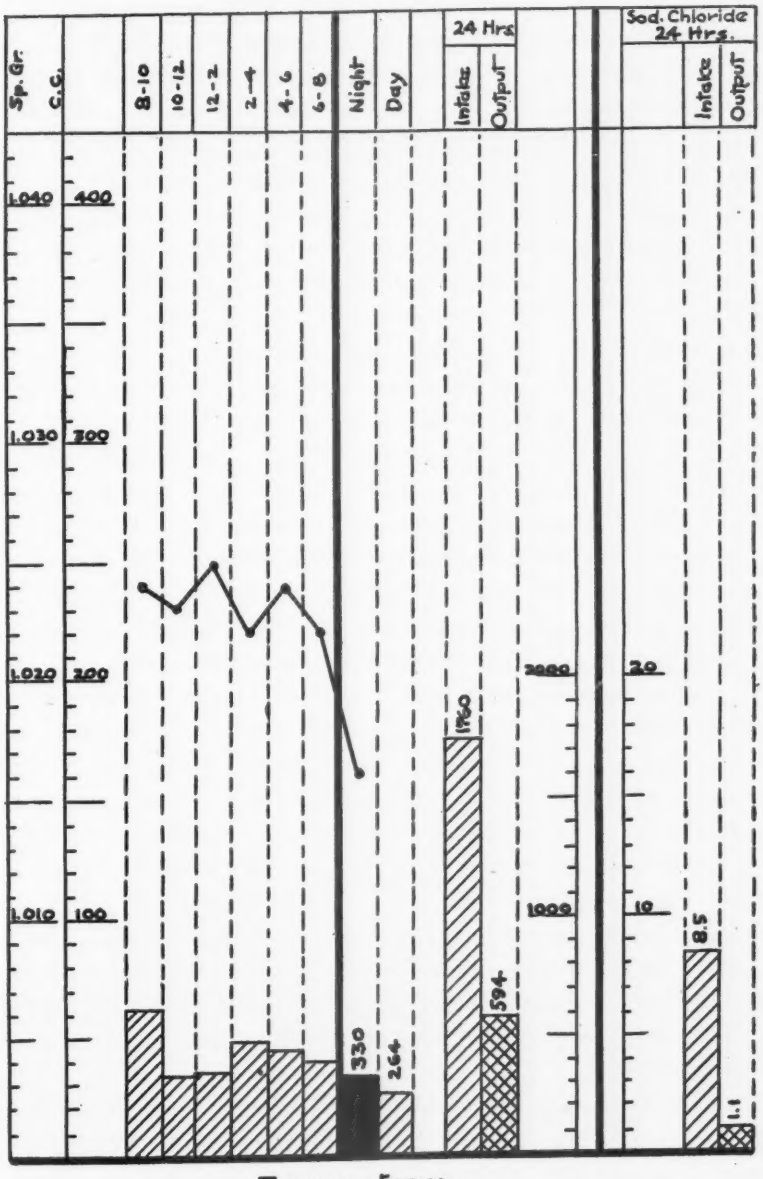

CHRONIC NEPHRITIS.

DIAGRAM III - CASE 5.




SLIGHT FUNCTIONAL ABNORMALITY.

DIAGRAM IV - CASE 14.



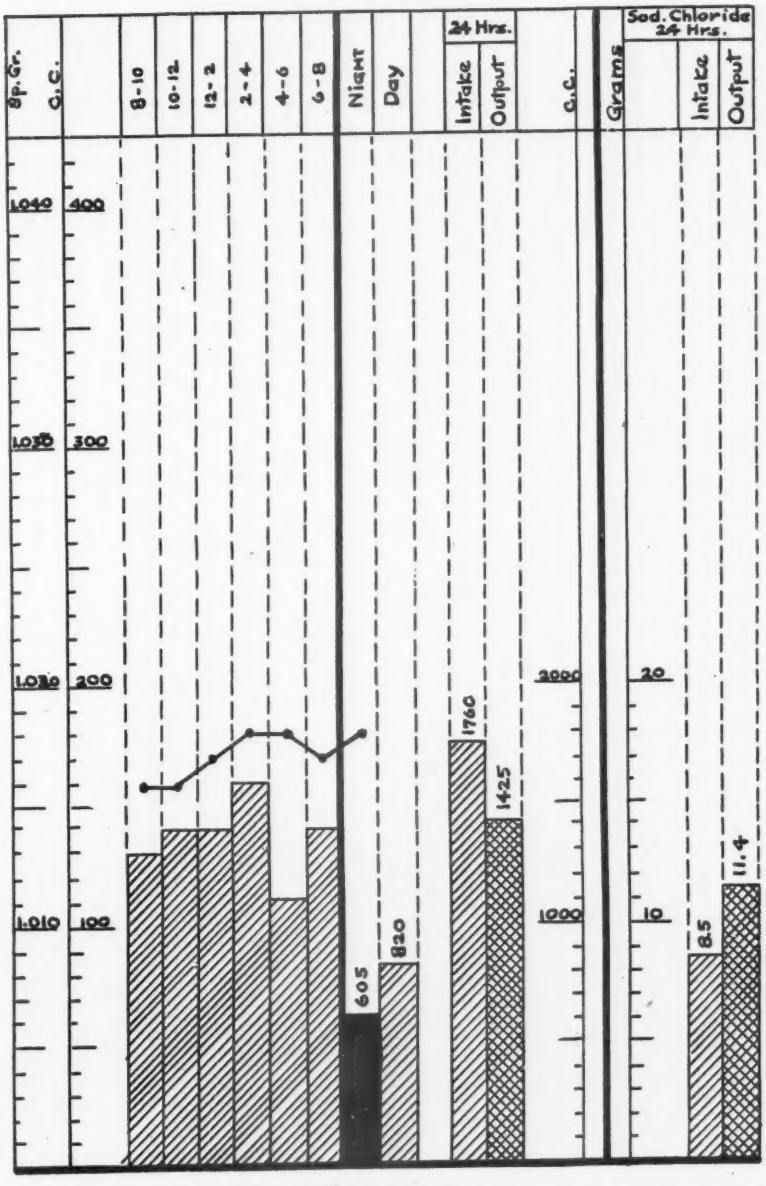

TERMINAL EDEMA.

cially of salt output. This is graphically shown in diagram IV. It is interesting to note that this same patient had received a functional test (diagram III, case 14) before the onset of the edema, at which time the output of salt was good (compare diagrams III and IV).

Group 3 contains two cases of bilateral renal tuberculosis, both diagnosed cystoscopically, and three other cases in which a tuberculous orchitis and suggestive urinary symptoms made a probability of accompanying renal tuberculosis. In case 10, although at the time of the test there were no renal symptoms, definite renal disease developed about eighteen months later. Case 7 died with uremic symptoms ten months after the test and an autopsy showed both kidneys to be completely involved by tuberculous lesions. The test in all of these cases indicates a very definite disturbance of function. The night urine is increased in four cases, with lowered specific gravity in three, but most characteristic of this group, occurring in all cases except 11, is a rather marked fixation of the specific gravity curve. This curve may be at a high level as in case 7 or at a low level as in case 8. Diagrams V, VI, and VII, representing cases 7, 8 and 10 illustrate these points. Mosenthal (13) obtained a picture very similar to this in cases of cystitis, pyelitis, and hypertrophied prostate. It is possible therefore that the picture in these cases of ours may have been influenced by tuberculosis elsewhere in the genito-urinary tract than the kidneys. Cystitis was not a common feature in any of these five cases, but we know that renal tuberculosis is almost always accompanied by more or less disease in the bladder. The two cases which were cystoscoped showed an accompanying cystitis but not of marked grade. The important fact however is that these cases of genito-urinary tuberculosis do show a characteristic change in the functional picture obtained by this test, whether this be due to renal or extra-renal causes The other renal tests in 3 of these cases have been discussed in the first series (see cases 5, 6, and 7), while in the other case tested (case 10) phthalein and blood urea were both normal. It would seem that Mosenthal's method, at least from a diagnostic standpoint, is of more value in these cases than the phthalein test.

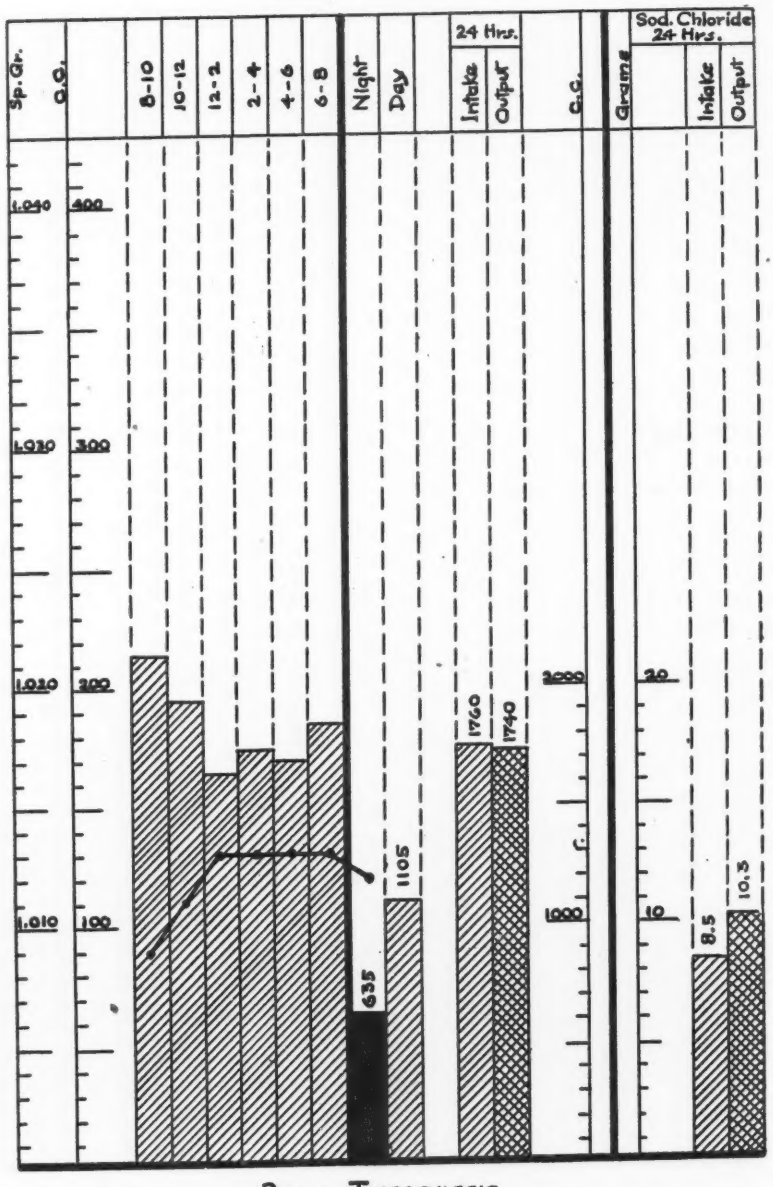
In group 4 the most interesting point is that in spite of the presence of albumin and casts in more than minimal amounts, 3 of the 7 cases showed a normal functon by this test, just as similar cases in the first series had by the phthalein and blood urea tests Two cases (13 and 14) showed an increased night urine and three of them (12, 14 and 17)

DIAGRAM V - CASE 7.



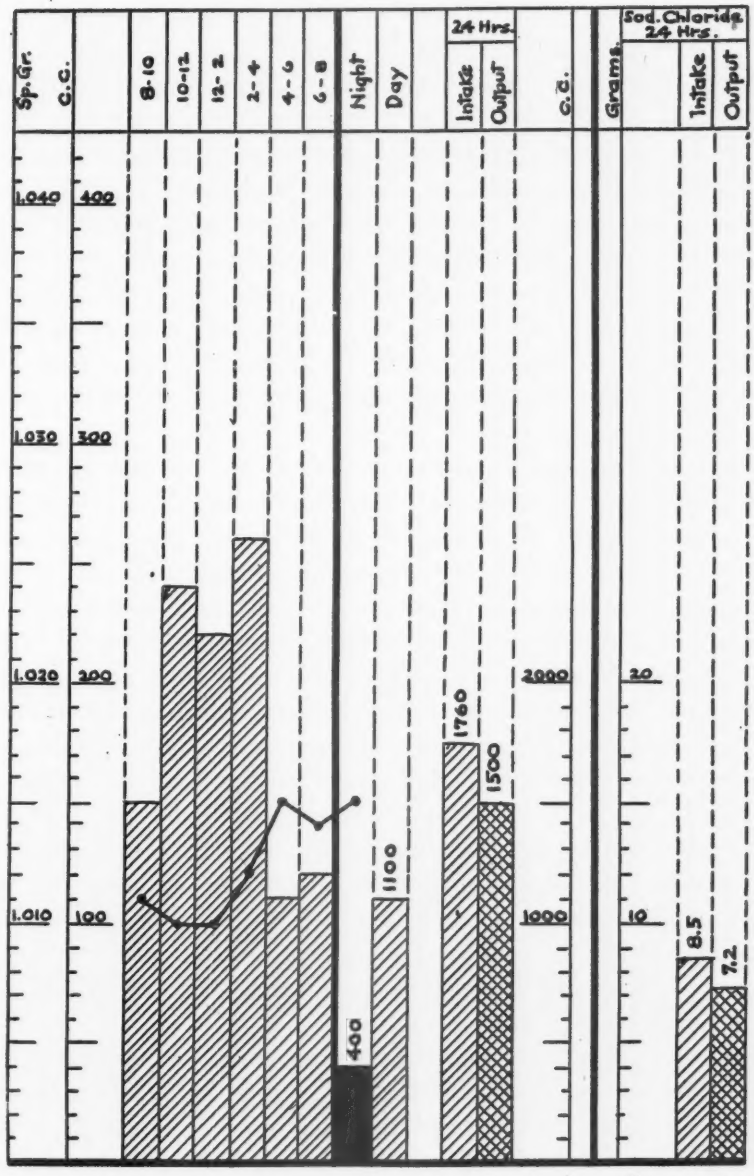

RENAL TUBERCULOSIS.

DIAGRAM VI - CASE 8.




RENAL TUBERCULOSIS.

DIAGRAM VII- CASE 10.




RENAL TUBERCULOSIS BEFORE DEVELOPMENT OF ANY CLINICAL SYMPTOMS.

a low night specific gravity. Case 13, as shown by subsequent developments (see discussion of case 5) probably had a parenchymatous nephritis.

In group 5, 13 of the cases showed normal function in spite of traces of albumin and casts. Three others (20, 21 and 35) showed only a low night specific gravity without other abnormality and one (19) an increased night urine of slightly low specific gravity. In three cases however (36, 37 and 38) a definitely abnormal picture was obtained. The night urine was large in amount, with a low specific gravity, and in cases 37 and 38 there was a fixation of the specific gravity curve. Clinically we did not find any evidence of nephritis or of genito-urinary tuberculosis, but the functional picture is so definite that we must conclude that there was some such factor. Unfortunately all of these cases left the sanatorium soon after this test, and before it had been followed up to any definite conclusions.

In group 6 three cases were normal while two (39 and 40) showed only a slightly lowered night specific gravity, so slight as to be probably without significance. A consideration of the last three groups would lead to the conclusion that the presence of albumin and casts, even in considerable amounts, does not necessarily indicate any disturbance of renal function, although it is not infrequently accompanied by such.

It seems worth while also to analyze this series from another standpoint, using the pulmonary instead of the renal condition of the patients as a basis for this purpose. Instead of using the ordinary classification of incipient, moderately, and far advanced, we have divided the patients into four groups of afebrile favorable cases, afebrile unfavorable, febrile unfavorable, and febrile very unfavorable. All of the patients in the last three groups and four in the first group were far advanced. We have excluded from this consideration the cases of nephritis and renal tuberculosis, since the results were in these cases obviously influenced by factors aside from the pulmonary disease. The thirty-two cases thus left may be divided as in table 4.

This table will indicate that the more advanced and unfavorable the stage of the pulmonary disease, the more apt is there to be a lowering of renal function. This lowered function however is usually of only such slight grade as to be of little significance. Even among the very unfavorable cases, we find three out of seven, or nearly half, with normal function. It would appear therefore that in pulmonary tuberculosis kidney function is as a rule only slightly if at all impaired, even in

far advanced very unfavorable cases. Fever appears to have no effect on kidney function, according to this test, for the unfavorable afebrile group 2 shows as many with lowered function as the unfavorable febrile group 3.

Finally the question comes up as to the value of these tests in routine pulmonary tuberculosis work, whether in sanatorium, hospital, or private practice. They are somewhat time consuming, and cause a certain amount of inconvenience to the patient, and we do not believe that it would be worth while to add them as a routine to the ordinary clinical and urinary tests, although they probably would, if so employed, occasionally bring to light an otherwise unsuspected disturbance of renal function, as in cases 36, 37, and 38 of our second series. In cases where there is any suspicion of nephritis, however, or especially of genito-urinary tuberculosis, either from history, symptomatology,

TABLE 4

| GROUP | PULMONARY CONDITION | FUNCTIONAL TEST | | | |
|---|---|---|---|---|---|
| | | Normal | Slight | Marked | Total |
| 1 | Afebrile, favorable | 8 | 2 | | 10 |
| 2 | Afebrile, unfavorable | 4 | 3 | 1 | 8 |
| 3 | Febrile, unfavorable | 4 | 2 | 1 | 7 |
| 4 | Febrile, very unfavorable | 3 | 3 | 1 | 7 |
| Total | | 19 | 10 | 3 | 32 |

clinical tests, or urinalysis, we are sure that they afford very valuable help and are well worth the effort required. In our experience Mosenthal's test is the most delicate of the lot, and if only one is used, should have preference. Of the other tests phenolsulphonephthalein is the most valuable. The lactose test we believe may be discarded without loss. The blood urea and Ambard tests are of unquestioned value but are so difficult and time consuming and apparently afford so little information that cannot be gained by the phthalein test, that we believe they may be reserved only for exceptional cases. Mosenthal's test and the phthalein test would therefore be recommended to be used under the conditions just mentioned.

## GENERAL CONCLUSIONS

1. In pulmonary tuberculosis, when unaccompanied by clinical evidence of renal disease, tests for renal function including phenolphthalein,

lactose, blood urea, Ambard's coefficient and Mosenthal's test meal show a normal or only slightly lowered function in all stages of the disease.

2. Slight lowering of function, sometimes found by Mosenthal's test, is more apt to be found in far advanced and unfavorable types of the disease than in favorable types.

3. Faint traces of albumin with or without a few hyaline casts appear to have no significance, so far as renal function is concerned. Albumin or casts in larger amounts are more frequently accompanied by slight lowering of renal function.

4. Renal tuberculosis, and apparently extra-renal genito-urinary tuberculosis, give a characteristic picture with Mosenthal's test which may be of help in diagnosis. The other tests in this condition show only slight if any indication of lowered function.

5. Chronic nephritis may occur as an independent complication of pulmonary tuberculosis, and, when present, an abnormal function is usually indicated by one or more of these tests.

6. Cases of terminal edema in pulmonary tuberculosis show a characteristic picture by Mosenthal's test, with a marked decrease in water and sodium chloride elimination. Whether this is due primarily to renal or cardiac conditions has not been determined.

7. A good working rule in pulmonary tuberculosis practice in regard to employing these tests would appear to us to be as follows: When there is any suspicion of nephritis or genito-urinary tuberculosis a Mosenthal test and a phthalein test should be made for the valuable diagnostic and prognostic help they may afford. In the absence of clinical symptoms of renal disease, if the urine shows albumin in amount beyond a trace, or casts other than a few hyaline, a Mosenthal test should be made. If this is positive the case should be kept under careful observation for the development of renal disease.

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# THE CULTIVATION OF TUBERCLE BACILLI FROM THE CIRCULATING BLOOD IN MILIARY TUBERCULOSIS[1].

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The occurrence of tubercle bacilli in the circulating blood in miliary tuberculosis has been recognized for a long time. The pathological anatomy of this disease indicates that tubercle bacilli must be distributed throughout the body from a primary focus by means of the blood stream. Even before the discovery of the tubercle bacillus, Villemin in 1868, and later others, produced tuberculosis in animals by inoculation with blood, first from experimentally infected animals, and later from tuberculous patients. Since that time, the presence of tubercle bacilli in the circulating blood of tuberculous patients has been proved by many investigators by the production of generalized tuberculosis in guinea-pigs inoculated with blood. The results obtained by a number of different authors are summarized in table 1.

As is shown in the table, there is a great discrepancy in the percentage of positive results obtained by different authors by the inoculation of guinea-pigs with blood. This may be explained in two ways:

First, in some cases, the diagnosis of tuberculosis in the inoculated guinea-pigs is unreliable. For example, in the series reported by Liebermeister many of the guinea-pigs reported as tuberculous died in from one to three weeks (or even less) after inoculation, obviously of acute intercurrent infection, without distinctively tuberculous lesions. No histological studies were reported, and the diagnosis was based on staining acid fast rods in smears from the bloody peritoneal exudate or from the organs. Some authors, for instance Kennerknecht, considered a guinea-pig tuberculous in the absence of gross lesions or histological changes if they found acid fast bacilli in the blood of the animal, or even in the sediment from the organs when digested with antiformin. Sturm even went so far as to call a guinea-pig tuberculous because he was able to find Gram positive bacilli and Much granules in the sedi-

[1] This work was done under the Mary Putnam Jacobi Fellowship of the Woman's Medical Association of New York City.

ment of the digested organs. In other reports, including those of Haga, Klemperer, and C. Fraenkel the character of the lesions found in the inoculated animals is not described, and it is impossible to draw any conclusions as to the reliability of the results.

Secondly, the type of cases studied differs in the different reports, some authors including only miliary tuberculosis in their statistics, and others only pulmonary or other types of tuberculosis. In this table the cases of miliary tuberculosis reported are separated from tuberculosis of other types, and included under a different heading.

In all, I have collected from the literature 1508 cases of tuberculosis studied by guinea-pig inoculation, of which 195 gave positive results. The percentage of positive results (12.9 per cent) in this series corresponds approximately to that obtained by Fischer in a compilation of 1250 cases with 17 per cent positive inoculations, by Fraenkel of 500 cases with 20 per cent positive results, and by Austrian and Hamman of 863 cases with 11 per cent positive inoculations. My figures are undoubtedly too high, because included in my table are the results of several investigators who were not sufficiently critical in their interpretation of tuberculous lesions in guinea-pigs. If the series of Liebermeister, Sturm, and Kennerknecht are omitted, there remain 1345 cases with 119 positive inoculations, approximately 8.8 per cent. Faber, selecting 1060 cases tested by guinea-pig inoculation with blood obtained during life, found only 4.2 per cent positive, while in 37 cases tested post mortem 38 per cent were positive.

If one considers only cases of miliary tuberculosis the percentage of positive guinea-pig inoculations with blood becomes much higher. Of 48 cases of miliary tuberculosis listed in table 1, 32 gave positive results, or 66.6 per cent. These figures are probably reliable because in nearly all instances gross lesions were reported in the inoculated animals. If the cases of miliary tuberculosis are subtracted from the total number there remain 1297 cases with 87 positive inoculations, a percentage of 6.7 for all types of tuberculosis other than miliary tuberculosis.

One may conclude, therefore, that the occurrence of tubercle bacilli in the circulating blood, at least in sufficient number to infect a guinea-pig, is relatively infrequent (6.7 per cent) in all forms of tuberculosis other than miliary tuberculosis, whereas in miliary tuberculosis, tubercle bacilli occur in the blood in a large percentage (66.6 per cent) of cases.

TABLE 1

*Tabular review of literature on guinea-pig inoculations with blood from tuberculous patients*

| AUTHOR | DATE | TOTAL CASES | | | MILIARY CASES | | | ANTE- OR POST-MORTEM | AMOUNT OF BLOOD INJECTED | TYPE OF TUBERCULOUS LESION PRODUCED | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total cases | Number positive | Per cent positive | Number of miliary cas s | Number positive | Per cent positive | | | | |
| | | | | | | | | | *cc.* | | |
| Meisel | 1884 | 8 | 8 | 100 | 8 | 8 | 100 | 1 A. M.<br>7 P. M. | Small amount of clot | Gross lesions | |
| Kühnau | 1897 | 12 | 1 | 8 | 4 | 1 | 25 | A. M. | | Not stated | |
| Jousset | 1903 | 6 | 2 | 33 | 0 | 0 | 0 | A. M. | | | |
| Bergeron | 1904 | 26 | 1 | 4 | 2 | 1 | 50 | A. M. | 5–10 | | |
| Gary | 1905 | 16 | 5 | 31 | 1 | 1 | 100 | A. M. | | All gross lesions | |
| Lüdke | 1906 | 14 | 5 | 35 | 2 | 2 | 100 | A. M. | 5–10 | Gross lesions. Tubercle bacilli stained in organs | 3 positive cases in advanced pulmonary tuberculosis |
| Huguenin | 1908 | 1 | 1 | 100 | 0 | 0 | 0 | P. M. | | | Blood of a foetus |
| Anderson | 1909 | 48 | 0 | 0 | 0 | 0 | 0 | A. M. | 2.5 | | 47 pulmonary cases with bacilli in sputum. One joint case. Parallel cultures negative |
| Dailey | 1909 | 17 | 0 | 0 | 2 | 0 | 0 | A. M. | 1–2 | | |
| Liebermeister | 1909 | 50 | 20 (?) | 40 | 0 | 0 | 0 | A. M. | 3–6 | Questionable gross lesions. Diagnosis in many cases depends on staining bacilli in peritoneal exudate | Pulmonary cases |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sturm..... | 1911 | 50 | 23 (?) | 46 | 0 | 0 | 0 | A. M. | 5 | Gross lesions in a few cases. Many results based on staining bacilli in sediment of digested organs. 3 cases seem certainly, and 4 probably positive. | |
| Fraenkel, C..... | 1912 | 50 | 7 | 14 | 0 | 0 | 0 | A. M. | | | Pulmonary cases |
| Bacmeister and Rueben..... | 1912 | 15 | 0 | 0 | 0 | 0 | 0 | A. M. | | | Incipient pulmonary cases |
| Kennerknecht.... | 1912 | 13 | 13 (?) | 100 | 0 | 0 | 0 | A. M. | Not given | Some gross lesions. Diagnosis mainly depended on staining bacilli in blood or organs of guinea pigs | |
| Liebermeister.... | 1912 | 50 | 20 (?) | 40 | 0 | 0 | 0 | A. M. | 3–6 | No protocols | Reports 100 cases with 40 positive results, including 50 already listed 1909 |
| Nobécourt and Darré..... | 1912 | 40 | 4 | 10 | 2 | 2 | 100 | | 10–20 cc. in 2–3 pigs | | 1 case tuberculous meningitis positive. 1 case acute tuberculous broncho-pneumonia positive |
| Rumpf..... | 1912 | 35 | 3 | 9 | 0 | 0 | 0 | A. M. | Not given | Not stated | |
| de Amicis..... | 1913 | 30 | 0 | 0 | 0 | 0 | 0 | A. M. | 5–9 | | Tuberculosis of lungs, glands, peritoneum, pleura, kidneys |
| Bacmeister..... | 1913 | 15 | 4 | 27 | 0 | 0 | 0 | A. M. | 10 | Gross lesions and stained smears | 4 positive only after a tuberculin reaction |
| Bernard et al.... | 1913 | 2 | 2 | 100 | 2 | 2 | 100 | | | | |
| Bogasau..... | 1913 | 41 | 0 | 0 | 0 | 0 | 0 | A. M. | Not stated | | "Phthisis" cases |

TABLE 1—*Continued*

| AUTHOR | DATE | TOTAL CASES | | | MILIARY CASES | | | ANTE- OR POST-MORTEM | AMOUNT OF BLOOD INJECTED | TYPE OF TUBERCULOUS LESION PRODUCED | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total cases | Number positive | Per cent positive | Number of miliary cases | Number positive | Per cent positive | | | | |
| | | | | | | | | | *cc.* | | |
| Dreesen..... | 1913 | 36 | 1 | 3 | 0 | 0 | 0 | A. M. | | | Also, 30 normals—all negative. Positive case advanced phthisis |
| Elsässer..... | 1913 | 25 | 0 | 0 | 0 | 0 | 0 | A. M. | | | All pulmonary cases |
| Fraenkel, E..... | 1913 | 24 | 2 | 8 | 0 | 0 | 0 | A. M. | Not stated | Gross lesions and stained smears | All pulmonary cases |
| Haga..... | 1913 | 81 | 24 | 30 | 0 | 0 | 0 | A. M. | 1–2.5 cc. in 4 pigs | Not stated | |
| Kachel..... | 1913 | 26 | 4 | 15 | 0 | 0 | 0 | A. M. | 4–5 | Gross lesions not extensive | One other pig gave a positive tuberculin reaction |
| Lange and Lindemann..... | 1913 | 78 | 1 | 1 | 0 | 0 | 0 | A. M. | | Not stated | Animal experiments not completed |
| Mayer..... | 1913 | 25 | 0 | 0 | 1 | 0 | 0 | A. M. | Not stated | | 24 pulmonary cases |
| Querner..... | 1913 | 37 | 0 | 0 | 0 | 0 | 0 | A. M. | 10 | | All pulmonary |
| Rist et al..... | 1913 | 50 | 0 | 0 | | | | | | | |
| Rothacker and Charon..... | 1913 | 46 | 1 | 2 | 1 | 1 | 100 | A. M. | 3 | Gross lesions | Several advanced pulmonary cases |
| de Verbizier.... | 1913 | 15 | 0 | 0 | 0 | 0 | 0 | A. M. | Sediment of 5 cc. | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baetge | 1914 | 29 | 8 | 27 | 0 | 0 | 0 | A. M. | 6 cc. each in 2 pigs. | Not stated. | 28 pulmonary. 1 meningitis negative. Only 1 of each pair of pigs died. |
| Fischer | 1914 | 13 | 0 | 0 | 2 | 0 | 0 | A. M. | 1–4 | | 2 miliary cases probably chiefly meningeal. |
| Haas | 1914 | 24 | 0 | 0 | 0 | 0 | 0 | A. M. | 6–7 | | Surgical cases. |
| Klemperer | 1914 | 25 | 6 | 24 | 2 | 2 | 100 | A. M. | 5 | Not stated. | 16 pulmonary cases, 2 positive, 1 pleurisy twice positive with recovery |
| Klopstock and Seligmann | 1914 | 49 | 0 | 0 | 0 | 0 | 0 | A. M. | 2 cc. in each of 2 pigs | Gross and microscopic | |
| Lehmann | 1914 | 104 | 6 | 6 | 2 | 1 | 50 | A. M. | 1–2 | Gross lesions | 1 tuberculosis of cheek and hand positive, 1 scrofula and healed bone tuberculosis positive, 2 occult tuberculosis positive, 1 pulmonary tuberculosis positive |
| Rautenberg | 1914 | 5 | 0 | 0 | 0 | 0 | 0 | A. M. | 5 | Injected apes and pigs | Advanced pulmonary cases |
| Seidenberger and Seitz | 1914 | 26 | 9 | 35 | 7 | 6 | 85 | P. M. | 5 | Gross lesions | |
| Storath | 1914 | 17 | 0 | 0 | 0 | 0 | 0 | A. M. | 5–10 | Gross and microscopic. All rabbits | Before and after tuberculin |
| Austrian | 1915 | 25 | 0 | 0 | 0 | 0 | 0 | A. M. | 4–7.5 | | Pulmonary cases |
| Hamman | 1915 | 20 | 0 | 0 | 0 | 0 | 0 | A. M. | 2.5–5 | | Pulmonary cases |
| Brown et al. | 1915 | 84 | 3 | 4 | 0 | 0 | 0 | A. M. | 8–10 | Gross lesions | Pulmonary cases |
| Moewes | 1915 | 80 | 9 | 11 | 10 | 5 | 50 | A. M. | 2.5–3.5 | Not given | 10 miliary cases |
| | | | | | | | | 1 P. M. | Some 20 | | 70 pulmonary cases |
| Rumpf and Zeissler | 1915 | 25 | 2 | 8 | 0 | 0 | 0 | | Not stated | Histological lesions | Pulmonary cases |
| Total | | 1508 | 195 | 12.9 | 48 | 32 | 66.6 | | | | |

The attempted demonstration of tubercle bacilli in the blood by means of stained smears needs little comment. Austrian and Hamman in 1915 published a detailed article with a fairly complete bibliography on the subject, and Berry in her article has good summaries of the earlier literature. Liebmann in 1891 reported the finding of tubercle bacilli in blood smears from tuberculin-treated patients. It was shown, however, that his findings were due to gross errors in technique. Interest in the subject was reawakened in 1909 by the publications of Rosenberger in this country and of Schnitter in Germany. Rosenberger reported the demonstration of tubercle bacilli in the blood in 100 per cent of a series of 49 cases, and later of 300 cases, by staining the organisms in the centrifugalized sediment from citrated blood. Schnitter used a modification of Stäubli's acetic acid method for the demonstration of parasites in the blood. After hemolyzing the red blood cells in acetic acid he digested the sediment, obtained by centrifugalization, with antiformin. He claimed to have found tubercle bacilli in smears from the sediment so obtained in 32 per cent of tuberculous cases.

Following these publications a large amount of work was done on the subject with very conflicting results. Kurashige even found tubercle bacilli in blood from apparently normal individuals. Parallel experiments with guinea-pig inoculations and staining methods did not, in most instances, give corresponding results. A source of error in these results was pointed out first by Brem, who demonstrated the frequent presence of acid fast bacilli in distilled water. This observation was later confirmed by other writers (Burvill-Holmes, Beitzke, A. Lehmann). Bacmeister and Rueben found that the chemical reaction of acetic acid and antiformin may cause appearances simulating acid fast bacilli, and Bernard, Debré, and Baron found acid fast granules in pure antiformin. These observations, together with the conflicting results obtained by parallel series of guinea-pig inoculations, indicate the unreliability of the method.

The frequent difficulty in the differential diagnosis of miliary tuberculosis from other non-tuberculous infections clinically, and the slowness and uncertainty of diagnosis by guinea-pig inoculation, suggested the use of cultural methods for the demonstration of tubercle bacilli in the blood.

A fairly extensive review of the literature reveals only one case in which tubercle bacilli have been cultivated from the blood of tuberculous patients. This was a case reported by Faber, who obtained a growth

of tubercle bacilli on a plain agar slant inoculated with blood from the heart of a child dead of generalized tuberculosis. Faber obtained negative cultures with 1 to 5 cc. of blood in 21 other cases of miliary tuberculosis in children, and negative cultures have been obtained from the blood by Brown, Heise, and Petroff in 22 pulmonary cases, and by Anderson in 47 pulmonary cases and 1 joint case. Positive cultures from the blood of experimentally infected guinea pigs and rabbits have been reported by Loewenstein, and later by Anderson.

The following method was used at first in my cultures, but was later modified in order to decrease the time necessary for growth to become apparent. Ten to 15 cc. of blood were aspirated with a syringe from a cubital vein and added to an equal volume of 1.5 per cent solution of sodium citrate to prevent clotting. Part of this blood was used for control guinea-pig inoculations in most of the cases. The remaining blood was added to shallow flasks of 5 per cent glycerine broth made neutral or slightly acid (phenolphthalein). After a preliminary incubation the contents of the flasks were centrifugalized and the sediment planted on blood agar slants. Human blood agar was used because it was simply and easily obtained. The slants were then sealed with paraffine to prevent drying, and incubated.

Positive results were obtained by this method in 3 cases.

*Case 1.* G. H., Med. 23207, colored boy, five years of age. A clinical diagnosis of acute miliary tuberculosis was made, though at first the clinical picture resembled that of typhoid fever. Autopsy diagnosis: Acute miliary tuberculosis with the primary focus in the mediastinal glands, rupturing into the azygos vein. Blood culture was obtained ten days before death. Three cubic centimeters of citrated blood were added to a flask of glycerine broth and incubated for six weeks. Smears made from the sediment in the flask at this time showed acid fast bacilli. The contents of the flask were then centrifugalized, part of the sediment planted on blood agar slants, and part injected intraperitoneally into each of 2 guinea-pigs. After three weeks a dry, wrinkled, slightly brownish growth was noted on the blood agar slants, and after six weeks one of the guinea-pigs died with generalized tuberculosis. Tubercle bacilli were demonstrated in smears from the subcultures, and from the organs of the guinea-pig, and were grown in culture from the spleen and liver of the guinea-pig. The other guinea-pig inoculated with the sediment died four days after the injection without tuberculous lesions.[2]

[2] This blood culture, and several of the cultures from other fluids included in table 2, were taken by Dr. Paul W. Clough, and the data in regard to them obtained, with his permission, from the hospital records.

*Case 2.* G. W., Med. 35610, white man, thirty-seven years of age. In this case also the clinical picture at first resembled that of typhoid fever, but the subsequent course made a definite diagnosis of miliary tuberculosis possible. Autopsy diagnosis: Fibrinous pleurisy, encapsulated apical pulmonary tuberculosis, bronchial lymphadenitis, caseous tuberculosis of the left adrenal, caseous mesenteric and retroperitoneal tuberculosis, rupture of a caseous gland into the cisterna chyli, generalized miliary tuberculosis, tuberculous meningitis and choroiditis, ulcer of the ileum. Fifteen cubic centimeters of blood were obtained in citrate solution fourteen days before death. A guinea-pig inoculated intraperitoneally with 3 cc. of the blood died a few days later without tuberculous lesions. Twelve cubic centimeters of the blood were added to several flasks of glycerine broth, and incubated for about five weeks. The contents of the flasks were centrifugalized, and the sediment planted on blood agar slants which were then sealed. About four weeks later numerous pinhead sized, buff-colored, dry colonies were noticed. Smears from the culture showed slender, acid fast bacilli, some curved and beaded, typical of the tubercle bacillus in their morphology and arrangement. Three guinea-pigs were injected with varying amounts of the culture, and all developed generalized tuberculosis. At autopsy all of the animals showed caseous tissue at the points of inoculation, extensive glandular enlargement with caseation in many of the glands, and caseous conglomerate tubercles in the spleens, which in two of the guinea-pigs were six to eight times the normal size. Two of the guinea-pigs showed also similar caseous tubercles in the liver. Typical tubercle bacilli were demonstrated in the glands, spleens, and livers of all the inoculated guinea-pigs. Subcultures from the original culture were made, and a characteristic growth appeared in about ten days. Smears from this growth showed typical tubercle bacilli in pure culture.

*Case 3.* J. E., H. L. H. Disp. 12893, white boy, six years of age, from the service of Dr. Howland. Clinical diagnosis: Acute generalized miliary tuberculosis, tuberculous meningitis, and tuberculosis of the choroid. No autopsy was made. X-ray examination showed miliary tuberculosis of the lungs. Tubercle bacilli were demonstrated by smears and by guinea-pig inoculation in the spinal fluid. Blood culture was made three days before death. Fifteen cubic centimenters of blood were obtained in citrate solution. Two guinea-pigs were inoculated in the left groin with 3.75 cc. of blood each. One guinea-pig lived four months, and when killed at the end of that time, showed no tuberculous lesions. The other guinea-pig remained healthy for four months and was then lost. The other half of the blood (7.5 cc.) was added to shallow glycerine broth flasks. After sixteen days the contents of the flasks were centrifugalized, the sediment planted on blood agar slants and the slants sealed. This culture was set aside after a short period of observation, and was not looked at again until six months later,

when a growth was noticed on one slant, in the water of condensation. Characteristic, large, buff-colored, dry colonies were present in the fluid, and also at the base of the slant where the water of condensation had washed over the slant. Smears from the growth showed an acid fast bacillus having the morphological features of the tubercle bacillus. An emulsion made from the growth was injected into two guinea-pigs. One of these died eighteen days later with a large caseous mass at the site of inoculation, enlarged but not caseous iliac, mesenteric, and bronchial glands, marked enlargement of the spleen which was studded with miliary tubercles, and consolidation of the left lung. Typical tubercle bacilli were demonstrated in smears from the spleen. The other guinea-pig died six weeks after inoculation with caseation at the point of injection, general glandular enlargement with caseation, and extensive miliary tuberculosis of the spleen and liver. Smears from the liver and spleen showed many tubercle bacilli. Subcultures from the original culture were made, and a typical growth appeared in about nine days.

In carrying out these cultures no attempt was made to make an early diagnosis of the cases by means of the cultures, and they were not watched carefully for the first appearance of growth. In order to make the cultures of practical value in diagnosis it seemed desirable to try methods which would yield growth in a shorter period of time. In the third case cited above, the appearance of growth in only one of the slants inoculated from the broth after sixteen days incubation suggested that very little multiplication had occurred in the broth. It was thought, then, that this preliminary incubation in broth might be dispensed with, and the following method was used. The blood was hemolyzed with distilled water, and the sediment after centrifugalization planted directly on blood agar slants which were sealed with paraffine.

Since there were no cases of miliary tuberculosis in the clinic at the time, the experiment was made with normal blood artificially seeded with a very small number of tubercle bacilli (G. W., third transfer). Ten cubic centimeters of blood were collected in the usual way, and the red blood corpuscles hemolyzed by the addition of distilled water. The blood was then centrifugalized at high speed for one and one-half hours, and the sediment planted on blood agar slants which were sealed with paraffine. In six days, growth became visible as small, semi-transparent colonies, which in eight days were somewhat larger and more opaque, and at the end of ten days were characteristic.

Growth in the culture direct from the body would probably have been somewhat slower in appearing than in this culture from the third transfer. Smears from the culture showed tubercle bacilli in pure culture.

Three positive cultures were obtained by the second method in 2

cases. In one of these cases 2 positive blood cultures were obtained, one ante mortem, and one from the heart's blood post mortem.

*Case 1.* E. M., H. L. H. Disp. 14950, colored girl, eight years of age, from the service of Dr. Howland. Clinical diagnosis: Generalized miliary tuberculosis, tuberculous meningitis. Autopsy diagnosis: Generalized tuberculous lymphadenitis, generalized miliary tuberculosis, tuberculous meningitis and peritonitis. Focus of dissemination not found. A blood culture was obtained one day before death. Twenty cubic centimenters of citrated blood were hemolyzed by the addition of distilled water. The blood was then centrifugalized and four-fifths of the sediment (representing 16 cc. of blood) was planted on blood agar slants. One-fifth of the sediment (from 4 cc. of blood) was injected subcutaneously into the groin of a guinea-pig. This animal died three months later from an intercurrent bronchopneumonia without tuberculous lesions. In this case hemolysis of the blood was incomplete, and the slants were covered with a rather thick layer of sediment. For this reason growth did not become evident for twenty-five days. Smears from this growth showed typical tubercle bacilli. A guinea-pig inoculated with a suspension of this growth died ten weeks later, and showed a general glandular enlargement with caseation in many of the glands, and a marked enlargement of the spleen which was full of tubercles. The nature of these lesions was confirmed by microscopical sections. Tubercle bacilli were grown from the spinal fluid in this case in ten days.

*Case 2.* Ten cubic centimeters of blood were obtained from the heart of the preceding case at autopsy, and cultured in the same way. Growth became evident thirteen days after the culture was made as small, colorless, non-characteristic colonies, and smears from the culture showed numerous tubercle bacilli. The spinal fluid obtained post mortem was also cultured. After thirteen days growth was noted as fair-sized, buff-colored, dry, rounded colonies.

*Case 3.* L. M., H. L. H. Disp. 15068, white girl, four years of age, from the service of Dr. Howland. Clinical diagnosis: Pulmonary tuberculosis, tuberculous meningitis, miliary tuberculosis (?). No autopsy was obtained. The blood was cultured one day before death. Ten cubic centimeters of blood were obtained in citrate solution, and the red blood cells laked by the addition of distilled water. After centrifugalization three-fourths of the sediment was planted on blood agar slants which were then sealed, and one-fourth of the sediment inoculated subcutaneously into the groin of a guinea-pig. After a week's incubation, minute, semi-transparent, colorless colonies became visible on some of the slants, and smears from these colonies showed clumps of typical tubercle bacilli. The guinea-pig inoculated with one-fourth of the sediment, died five and one-half weeks later and showed caseous areas in the

regional and iliac glands. Tubercle bacilli were demonstrated in smears from these glands. A guinea-pig inoculated with a suspension of the growth is still alive after three weeks, but shows marked enlargement of the regional glands. An exploratory operation showed extensive caseation of the regional glands, and marked enlargement of the spleen which was firm and apparently studded with small tubercles. The spinal fluid from this case was also cultured, and definite colonies appeared in a week.

By this method of cultivation positive results have been obtained from the blood in a relatively short time in 2 cases. A tentative diagnosis might have been made even before the appearance of visible growth by means of smears if sufficient multiplication had occurred. When the colonies first appear they are not characteristic, and smears must be made before an absolute diagnosis can be made. It may be a long time before the growth becomes as profuse as that of old laboratory strains, or this may occur only after repeated transfers. In the first case, the sediment obtained after laking the blood, when spread over blood agar slants, was so thick that growth did not become recognizable for twenty-five days. In order to obtain positive cultures in the shortest possible time, (therefore making the method more useful as a diagnostic procedure), it may be desirable to reduce the bulk of the sediment still further by digestion with antiformin (as originally suggested by Uhlenhuth and Kersten for cultures from sputum and other tuberculous material) and to inoculate the washed sediment directly on blood agar. This method would also be of value if the blood had accidentally become contaminated, or in the case of autopsy blood cultures where post mortem invasion of the blood by the other organisms may have occurred. Blood cultures done by this method are in progress at the present time. It is also possible that the use of other media such as Dorset's egg medium, or glycerine beef agar, might give positive results in a shorter period of time and in a larger percentage of cases. Human blood agar was used in my cultures because it was easily available.

Negative blood cultures by one or another of these methods were obtained in 2 out of the 7 cases of acute miliary tuberculosis studied. In one of these cases only 2 cc. of blood were available for culture, and 1 cc. for guinea-pig inoculation. The guinea-pig has remained healthy for three months, and has no enlargement of the inguinal glands.

Negative blood cultures were obtained in 9 cases of other types of tuberculosis, and guinea-pig inoculations done in 4 of these cases were negative as well. Of these cases one was tuberculous peritonitis; a

TABLE 2

*Cultures from tuberculous fluids*

| NAME | HOSPITAL NUMBER | AGE | DIAGNOSIS | AUTOPSY | SMEARS | CULTURE | | GUINEA-PIG INOCULATION | | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Result | Interval | Result | Interval | |
| Blood cultures | | | | | | | | | | |
| G. H. | Med. 23207 | 5 | Miliary tuberculosis | Yes | Not done | Positive | 2½ months | Not done | | Guinea pig inoculated with culture developed tuberculosis. 1 guinea pig died prematurely |
| G. W. | Med. 35610 | 37 | Miliary tuberculosis. Tuberculous meningitis | Yes | Not done | Positive | 2½ months | Done. Guinea pig died prematurely | | Guinea pig inoculated with culture developed tuberculosis |
| J. E. | H. L. H. Disp. 12893 | 6 | Miliary tuberculosis. Tuberculous meningitis | No | Not done | Positive | 5 months | Negative. 2 guinea pigs inoculated. Both remained well | | Guinea pig inoculated with culture developed tuberculosis |
| E. M. | H. L. H. Disp. 14950 | 8 | Miliary tuberculosis. Tuberculous meningitis | Yes | Not done | Positive | 25 days | Negative. 1 guinea pig inoculated. Died after 3 months without tuberculous lesions | | Guinea pig inoculated with culture developed tuberculosis. Spinal fluid culture positive |
| E. M. | H. L. H. Disp. 14950 | 8 | Miliary tuberculosis. Tuberculous meningitis | Yes | Not done | Positive | 13 days | Not done | | Blood culture made post-morten. Spinal fluid culture positive |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| L. M. | H. L. H. Disp. 15068 | 4 | Miliary tuberculosis. Tuberculous meningitis | No | Not done | Positive | 7 days | Positive | 5½ weeks | Guinea-pig inoculated with culture developed tuberculosis. Spinal fluid culture positive |
| H. L. | H. L. H. Disp. 14215 | 7 mos. | Miliary tuberculosis. Tuberculous meningitis. Pulmonary tuberculosis | Yes | Not done | Negative | | Negative Guinea pig well after 5 months | | Only 2 cc. of blood obtained. Spinal fluid cultures positive |
| S. Ht. | Med. 23684 | 26 | Miliary tuberculosis. Tuberculous meningitis. Pulmonary tuberculosis | Yes | Negative | Negative | | Negative | | Spinal fluid culture positive |
| W. S. | Med. 36896 | 18 | Tuberculous peritonitis | Yes | Not done | Negative | | Not done | | |
| E. L. | Med. 24140 | 5 | Pulmonary tuberculosis. Tuberculous adenitis | No | Not done | Negative | | Not done | | |
| C. M. | Med. 23487 | 24 | Pulmonary tuberculosis | No | Not done | Negative | | Not done | | |
| W. M. | Med. 23576 | 23 | Pulmonary tuberculosis | Yes | Not done | Negative | | Not done | | Spinal fluid culture negative |
| M. S. | H. L. H. Disp. 13349 | 3 | Tuberculous meningitis | Yes | Not done | Negative | | Negative | | Few old tubercles in organs at autopsy |
| C. T. | Med. 24277 | 8 | Tuberculous meningitis | Yes | Not done | Negative | | Not done | | Spinal fluid culture, positive |
| M. H. | Med. 23799 | 20 | Tuberculous meningitis | Yes | Not done | Negative | | Negative | | Spinal fluid culture, negative |
| S. Hn. | Med. 23508 | 5 | Tuberculous meningitis | No | Not done | Negative | | Negative | | Spinal fluid culture, positive |
| J. J. | H. L. H. Disp. 15178 | 1 | Pulmonary tuberculosis. Tuberculous meningitis | No | Not done | Negative | | Negative | | Spinal fluid culture, positive |

TABLE 2—*Continued*

| NAME | HOSPITAL NUMBER | AGE | DIAGNOSIS | AUTOPSY | SMEARS | CULTURE | | GUINEA PIG INOCULATION | | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Result | Interval | Result | Interval | |
| | | | | | Spinal fluids | | | | | |
| S. Hn. | Med. 23508 | 5 | Tuberculous meningitis | No | Not done | Positive | 5 weeks | Not recorded | | 1 negative, and 2 positive cultures |
| S. Ht. | Med. 23684 | 26 | Miliary tuberculosis. Tuberculous meningitis | Yes | Positive | Positive | 5 weeks | Positive | | 2 positive cultures. Blood culture negative |
| M. L. | Med. 23922 | 2 | Tuberculous meningitis | No | Not done | Positive | 4 weeks | Not done | | |
| J. F. | Med. 24005 | 2 | Tuberculous meningitis | No | Positive later | Positive | 3–4 weeks | Not done | | First culture negative, 2 positive cultures |
| B. A. | Med. 24036 | 8 | Tuberculous meningitis | Yes | 2 negative | Positive | 3 months | Not done | | 2 positive cultures. |
| O. H. | Med. 24110 | 17 | Tuberculous meningitis. Miliary tuberculosis. Tuberculosis of spine | Yes | Negative | Positive | 2 months | Not done | | |
| G. R. | Surg. 24203 | 8 | Tuberculous meningitis | Yes partial | Negative | Positive | 5 weeks | Not done | | |
| C. T. | Med. 24277 | 8 | Tuberculous meningitis | Yes | Negative | Positive | 3 weeks | Not done | | |
| J. J. | H. L. H. Disp. 15178 | 1 | Tuberculous meningitis. Pulmonary tuberculosis | No | Negative | Positive | 6 weeks | Positive | 3 months | |
| E. C. | Med. 38345 | 41 | Tuberculous meningitis. Pulmonary tuberculosis | No | Negative | Positive | 6 weeks | Done. Guinea-pig died prematurely | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| H. L. | H. L. H. Disp. 14215 | 7 mos. | Tuberculous meningitis. Miliary tuberculosis | Yes | Positive | Positive | 11 days | Not done | | Guine-pig inoculated with culture developed tuberculosis |
| E. M. | H. L. H. Disp. 14950 | 8 | Tuberculous meningitis. Miliary tuberculosis | Yes | Negative | Positive | 10 days | Not done | | Guinea-pig inoculated with culture developed tuberculosis. Blood culture positive |
| L. M. | H. L. H. Disp. 15068 | 4 | Tuberculous meningitis. Miliary tuberculosis | No | Positive | Positive | 7 days | Positive | 3 weeks | Guinea-pig showed tuberculosis only in regional and iliac glands. Blood culture positive |
| R. A. | H. L. H. Disp. 2945 | 4 | Tuberculous meningitis. Miliary tuberculosis | No | Positive | Positive | 7 days | Positive | 4 weeks | Guinea-pig showed tuberculosis only in regional and iliac glands |
| W. G. | Med. 23453 | 5 | Tuberculous meningitis | No | Not done | Negative | | Not done | | |
| M. H. | Med. 23799 | 20 | Tuberculous meningitis | Yes | Negative | Negative | | Not done | | Blood culture negative |
| | | | | | Pleural fluids | | | | | |
| D. M. | Med. 23118 | 21 | Pleurisy with effusion. Pulmonary tuberculosis? | No | Negative | Positive | 2 | Positive | 2 months | |
| D. K. | Med. 23144 | 13 | Pleurisy with effusion. Pulmonary tuberculosis? | No | Negative | Negative | | Negative | | |
| J. C. | Med. 23167 | 35 | Pleurisy with effusion | No | Negative | Negative | | Negative | | |
| A. S. | Med. 23365 | 51 | Pleurisy with effusion | No | Not done | Negative | | Negative | | |

TABLE 2—*Concluded*

| NAME | HOSPITAL NUMBER | AGE | DIAGNOSIS | AUTOPSY | SMEARS | CULTURE | | GUINEA-PIG INOCULATION | | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Result | Interval | Result | Interval | |
| **Peritoneal fluids** | | | | | | | | | | |
| W. W. | Med. 23717 | 35 | Cirrhosis of liver. Chronic gastritis | | | Negative | | Negative | | Probably not tuberculous |
| **Pericardial fluids** | | | | | | | | | | |
| J. L. | Med. 23393 | 33 | Syphilis of aorta with multiple aneurisms. Chronic adhesive pericarditis. Pleurisy with effusion etc. | Yes | | Negative | | Negative | | Probably not tuberculous |
| **Joint fluids** | | | | | | | | | | |
| J. C. | Surg. 23121 | 58 | Tuberculous arthritis of knee. Pulmonary tuberculosis | Tissue at operation tuberculous | Positive | Positive | 3 weeks | Guinea-pig died in 10 days without lesions | | |
| F. D. | Surg. 23960 | 20 | Villous arthritis of knee | No | Not done | Positive | 3 months | Not done | | |
| S. W. | Surg. 24214 | 47 | Tuberculous arthritis of ankle | No | Not done | Negative | | Not done | | |
| **Abscess of rib** | | | | | | | | | | |
| L. C. | Surg. 23966 | 50 | Tuberculosis of rib. Abscess of chest wall, tuberculous | Tissue tuberculous | Not done | Positive | 4 weeks | Not done | | |
| **Abscess of neck** | | | | | | | | | | |
| J. L. | Surg. 24168 | 63 | Abscess of neck tuberculous. Healed tuberculosis of hip | No | Not done | Positive | 6 weeks | Not done | | Abscess probably arising in sternoclavicular joint |

second, an acute tuberculous bronchopneumonia, a third; a chronic pulmonary tuberculosis in the second stage; a fourth, a pulmonary tuberculosis with adenitis and tabes mesenterica; and the remaining five, cases of tuberculous meningitis.

Cultures from the sediment obtained by centrifugalizing other tuberculous fluids have also been made by planting the sediment directly upon blood agar slants and sealing them. The results of these cultures, and of control smears and guinea-pig inoculations when made, are recorded in table 2.

In the work summarized in table 2 no attempt was made to watch the cultures for the earliest date at which growth appeared except in the last 4 positive spinal fluid cultures in the table, and parallel smears and guinea-pig inoculations were not done in every case. Of the 16 spinal fluid cultures 2 were negative and 14 were positive. In 7 of the cases positive by culture, tubercle bacilli could not be demonstrated in smears. Four pleural fluids were cultured with 1 positive result. Smears from this positive case were negative, but a guinea-pig inoculated with the fluid developed generalized tuberculosis. The 3 negative cases were negative also by guinea-pig inoculation, and 2 of the 3 by smears as well. Tubercle bacilli were grown in culture from 2 out of 3 fluids from tuberculous joints, and from the pus from an abscess of a rib, and an abscess of the sternum. One peritoneal fluid and 1 pericardial fluid were negative by culture and by guinèa-pig inoculation. Both of these cases were probably not tuberculous.

## SUMMARY AND DISCUSSION

In this work tubercle bacilli have been grown in culture for the first time from the circulating blood of 5 patients with miliary tuberculosis.

In the first method used the blood was added to glycerine broth flasks, and after a preliminary incubation the sediment was planted on blood agar slants, which were sealed and incubated. Three positive cultures were obtained by this method. In order to shorten the period of time necessary for growth to become visible, a second method was tried in which the blood was hemolyzed with distilled water and the centrifugalized sediment planted directly on blood agar slants. Three positive cultures were obtained from 2 patients by this method in twenty-five, thirteen, and seven days. In order to reduce still further the bulk of the sediment, and hence the period of time necessary for growth to

become visible, a third method is suggested, consisting in the digestion of the sediment by means of antiformin. Further work is being done with this method.

In order to be of value, cultural methods for the demonstration of tubercle bacilli in the blood must give positive results sooner and more constantly than the method of guinea-pig inoculation. The data at hand are insufficient to permit any definite conclusions, and further work is being done as cases are available to determine these points. The experiment with the artificially seeded blood culture, and the three positive cultures obtained by the second method, indicate that growth may be obtained with appropriate methods in from one to three weeks. This is considerably under the time within which a positive result could often be obtained by guinea-pig inoculation. The injection of blood subcutaneously into the groin of a guinea-pig produces an induration which will mask the development of a moderate glandular enlargement for several weeks, and prevent an early diagnosis of inoculation tuberculosis in this way. Furthermore, tuberculosis produced in guinea-pigs by the injection of blood containing tubercle bacilli may be very slow in developing, as claimed by Marmorek in his work with experimentally infected guinea-pigs, and by others, using the blood of human cases (Baetge, Rumpf and Zeissler).

As regards the relative constancy with which results can be obtained by culture and by guinea-pig inoculation, nothing definite can yet be said. Under favorable cultural conditions, one might expect that one organism in the blood would produce a growth, while an appreciable number (varying inversely with the virulence) are needed to infect a guinea-pig. In the third case in my series half of the blood was injected into 2 guinea-pigs, neither of which became infected, while growth was obtained from the cultured half; and in the fourth case in which the blood culture was positive, the guinea-pig, inoculated with one-fifth of the blood obtained, died of intercurrent disease at the end of three months with no evidences of tuberculosis. Furthermore, guinea-pigs may die too soon for the development of macroscopic or microscopic lesions, either from the effects of the injection or from some intercurrent disease. This occurred in four of the control guinea-pig inoculations, one with blood, one with spinal fluid, one with joint fluid, and one with culture. The evidence at hand, then, would indicate that suitable cultural methods will probably yield positive results more promptly and more regularly than animal inoculations.

The methods of demonstrating tubercle bacilli in the blood by means of smears have been shown to be unreliable, but when cultures are obtained from the blood we have conclusive evidence of the existence of a bacillemia.

On the other hand smears made from clear fluids with relatively little sediment frequently give reliable results by direct staining methods. In this series, however, tubercle bacilli were demonstrated more frequently by culture than by smears, as one would expect with favorable cultural conditions if the number of organisms is small. In the examination of one pleural fluid and seven spinal fluids for tubercle bacilli by smears and by culture, the smears were negative while the cultures were positive. In no instances were smears positive without the culture being positive also.

The practicability of blood cultures as a diagnostic method will depend upon the frequency with which the tubercle bacillus enters and persists in the blood stream. That bacillemia occurs frequently in miliary tuberculosis is shown by the high percentage (66.6 per cent) of positive results obtained by various authors in these cases by the method of guinea-pig inoculation with blood (table 1), and by the relatively large number of positive cultures obtained in the small series reported here (5 out of 7 cases). On the contrary this is probably a relatively uncommon phenomenon in pulmonary, and other forms of localized tuberculosis. Out of 1297 cases collected in table 1 only 6.7 per cent of guinea-pig inoculations with blood gave positive results, and in my series all of the blood cultures in these cases were negative.

In spite of the large amount of work which has been done on the subject of bacillemia in tuberculosis there is very little information which is based upon reliable methods of study. It has been shown definitely that tubercle bacilli may enter the blood stream, but relatively little is known as to the conditions in which bacillemia occurs, its frequency and regularity, the number of organisms present, or its diagnostic or prognostic significance.

The conditions in experimental tuberculosis in animals are somewhat better understood because the exact pathological lesions present can be determined, and to a certain extent controlled. The bacillemia following the injection of tubercle bacilli has been studied by various investigators by the inoculation of guinea-pigs with blood from the infected animals. Some authors (for example, Moewes) obtained positive inoculation tuberculosis by the injection of blood from experimentally in-

fected animals in a large percentage of cases, while others in similar experiments obtained negative results (Sawyer). These divergent results are probably to be explained partly by differences in the virulence of the infecting organism, in its dosage and mode of administration, and in the time elapsing after inoculation before blood was withdrawn for the test. Marmorek in 1907 published a detailed report upon this point. He found that after intravenous injection into guinea-pigs, the bacilli disappear from the blood after one to two days and recur four to six weeks later; after arterial inoculation they disappear after one to two days and recur from five to fourteen days later. After subcutaneous inoculation bacilli appear for the first time in the blood after thirty to sixty days; following inoculation into the anterior chamber of the eye, somewhat sooner; and still earlier (fourteen to twenty days) after intraperitoneal injection. The relation of the virulence of the bacilli injected to their persistence in the circulation was studied by Hess, who found that the feebly virulent strains persist less long in the circulation after inoculation, and reappear later than do virulent strains.

Tuberculosis as it commonly occurs in man is not exactly analogous to that produced experimentally in animals, and a similar study of the bacillemia in human tuberculosis would be desirable. Blood cultures repeated at frequent intervals, supplemented, perhaps, by guinea-pig inoculations, would seem to offer a favorable method for determining not only the existence of a bacteriemia, but, approximately at least, the number of organisms present.

Blood cultures, then, are suggested as an aid in the differential diagnosis of acute miliary tuberculosis from other non-tuberculous infections, and as a means of studying bacillemia in all forms of tuberculous disease. Direct cultures from spinal, pleural, peritoneal, and other fluids are recommended in those cases in which tubercle bacilli cannot be demonstrated by smears.

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# STANDARDS FOR THE DIAGNOSIS, CLASSIFICATION AND TREATMENT OF TUBERCULOSIS IN CHILDREN AND ADULTS

COMMUNITY HEALTH AND TUBERCULOSIS DEMONSTRATION OF THE NATIONAL ASSOCIATION FOR THE STUDY AND PREVENTION OF TUBERCULOSIS

*Framingham, Massachusetts*

## FOREWORD

In the diagnosis of tuberculosis the greatest difficulties are met in the problems of childhood, and also in the questions involved in the determination of a diagnosis in adult cases where tubercle bacilli are not to be found in the sputum.

As part of an effort to simplify and standardize these diagnostic problems, Dr. Edward R. Baldwin of Saranac Lake, acting in his previous capacity as president of the National Association for the Study and Prevention of Tuberculosis, appointed a special committee known as the Diagnostic Standards Committee. This committee, working in cooperation with the representatives of the Community Health and Tuberculosis Demonstration in Framingham, after several sessions, has prepared a set of standards for diagnosis.

These diagnostic suggestions have been approved by the National Committee in charge of the Framingham work, and are now submitted to the physicians of Framingham for a practical test. In their present printed form, it is hoped that they may also elicit the criticism and suggestions of physicians interested in tuberculosis work elsewhere.

The Diagnostic Standards Committee not only attempted to meet the needs in the special fields of diagnosis mentioned above, but has also made an effort to clarify somewhat the standards for treatment in the several stages of the disease. Finally, the committee has recommended for use in Framingham the National Tuberculosis Association classification, with modifications suggested by Dr. W. L. Rathbun of Otisville Sanatorium, New York.

It is hoped that the somewhat novel arrangement of these recommendations into first, definitions, and second, minimum standards, will

prove practical and helpful. As far as Framingham is concerned, such a standardization would seem to have at least two distinct values. In the first place, it ought to be of practical importance to the physicians of Framingham. Further, uniformity in this regard is essential to the scientific aspects of the Community Health and Tuberculosis Demonstration, if the results throughout a period of several years are to be at all comparable.

The recommendations have been submitted to the physicians of Framingham through the Framingham Medical Club, and are now being experimented with by the Community Health Station examiners, the Board of Health Tuberculosis Dispensary, and the private physicians in Framingham. As a result of this trial, either in their present or modified form, it is hoped that they may subsequently prove of general use.

*The Community Health and Tuberculosis Demonstration National Committee:* Dr. Edward R. Baldwin, *Chairman;* Dr. Chas. L. Minor, Dr. Charles J. Hatfield, Mr. Homer Folks, Dr. Lee K. Frankle, Dr. Arthur K. Stone, Dr. Eugene R. Kelley, Dr. Stephen J. Maher, Dr. William Chas. White, Mr. Henry S. Dennison, Dr. Victor Safford, Dr. F. C. Smith.

*The Diagnostic Standards Committee:* Dr. Arthur K. Stone, *Chairman;* Dr. Edwin A. Locke, Dr. Cleveland Floyd, Dr. John B. Hawes, 2nd, Dr. Elliott Washburn, Dr. Vincent Y. Bowditch, Dr. Eugene R. Kelley, Dr. Herbert C. Clapp, Dr. Roger I. Lee, Dr. Richard Smith.

*Executive Officer:* D. B. Armstrong, M. D.

## THE DIAGNOSIS OF THORACIC (PULMONARY, BRONCHIAL GLAND, ETC.) TUBERCULOSIS IN CHILDHOOD

### *Definitions*

*1. Loss of weight.* By loss of weight should be understood an unexplainable loss of at least 5 per cent below normal limits for that particular child, or an unexplainable failure to gain weight over a period of four months.

*2. Loss of strength.* By loss of strength in its pathological sense is meant ease of tire and lack of staying power which are unusual for that individual child and which cannot be satisfactorily explained.

*3. Fever.* In young children rectal temperatures alone are dependable. To constitute fever in its pathological sense in childhood there

must be a more or less *constant* elevation of temperature over 100 degrees, taken at various times during the day and lasting over a period of at least one week. In older children temperature rules for adults apply.

*4. Elevation of pulse.* No definite standards can be laid down as to what constitutes elevation of pulse, as this varies according to the age. Observation should be over a longer period, and a wider latitude allowed, than in adults, before attaching significance to this as a symptom in childhood.

*5. Hemorrhage.* As in adults, any amount of blood, with or without sputum, requires medical investigation as to its source. This is a rare symptom in childhood.

*6. Family history.* An occasional case of tuberculosis in the patient's uncles, aunts, cousins, etc., should not be considered of importance, unless there has been intimate exposure and personal contact with such a case. It is an important fact, however, when the patient's immediate relatives, as *mother, father, brother, sister, nurses, nursemaids, attendants*, etc., have been tuberculous, and especially so when there has been prolonged and intimate contact.

*7. Exposure.* Exposure to tuberculosis, no matter how slight, from human sources or from milk and milk products is of very great importance. Prolonged exposure, especially under unhygienic habits or surroundings, is of still greater importance. This question should be gone into with the utmost care.

*8. Cough.* No cough is characteristic of tuberculosis in childhood. Persistent cough for six weeks requires investigation. Tuberculosis can and often does exist without any cough whatsoever. In certain cases of bronchial gland tuberculosis there may be a brassy, strident, paroxysmal cough resembling that of pertussis.

*9. Sputum.* Sputum, if present, should be examined. It is comparatively rare in tuberculosis in childhood.

*10. Hoarseness.* Any huskiness or persistent hoarseness requires investigation. This is likewise rare in childhood.

*11. Rales.* Rales are not to be regarded as essential in diagnosis and are not in themselves alone evidence of tuberculosis. In fact by the time rales are found in tuberculosis in childhood the disease is usually advanced and the diagnosis only too evident.

*12. Dulness.* Only very light percussion should be used. Dulness is not to be looked for at the apices as in adults, but over both sides of

the sternum (parasternal dulness), and between the scapulae (interscapular dulness.)

*13. Altered voice and breath sounds.* Pure bronchial breathing and egophony are comparatively rare in tuberculosis in childhoood. Harsh, prolonged, high pitched expiration and an intense whispered voice are often present. The whispered voice and not the spoken voice should be used.

*14. D'Espine's sign.* Intense whispered voice heard below the third dorsal vertebra is considered by many as abnormal and indicates the presence of enlarged bronchial glands. Such glands are not necessarily tuberculous, however.

### *Minimun standards*

On the basis of these definitions the following minimum standards in the diagnosis of active tuberculosis in childhood have been formulated:

1. Given a definite history of exposure, either from *bovine* or *human* sources, any symptoms, constitutional or local, require the most careful investigation, although they may not necessarily be due to tuberculosis.

2. Constitutional signs and symptoms of disease, such as loss of weight and strength, fever, etc. are of more importance than signs and symptoms relating to the chest.

3. Other causes for constitutional signs and symptoms, such as diseased tonsils or adenoids, carious teeth, improper feeding, rickets, etc., should be investigated before these signs and symptoms are attributed to tuberculosis.

4. The presence of tuberculosis elsewhere in the body, such as glands, bones, joints, etc., is not necessarily indicative of tuberculosis in the chest, nor is it true that these forms of tuberculosis convey immunity against pulmonary disease.

5. There may be extensive signs in the lungs, such as dulness, rales, altered voice and breath sounds, without these being due to tuberculosis. On the other hand, active tuberculosis may be present without definite signs and symptoms in the lungs.

6. Tuberculin tests. The Von Pirquet skin test is the best to use. When this test, properly applied, has been repeatedly negative on three trials, except during or after an attack of measles, or in the presence of far advanced tuberculous disease, tuberculosis may be ruled out. A positive skin test in children under five years of age may be indicative

of tuberculous disease, and points to the necessity for further observation. The diagnostic value of a positive tuberculin test becomes progressively less important, as significant of active disease rather than infection, in the years from five to fourteen.

7. A definite history of exposure, with a positive tuberculin reaction, accompanied by constitutional signs and symptoms, establishes a diagnosis of tuberculosis, even if the signs in the chest are vague, indefinite or absent. A similar history of exposure, even with a positive tuberculin reaction, but without constitutional signs and symptoms and without definite signs in the chest, does not justify a diagnosis of tuberculous disease, but merely of tuberculous infection, except in very young children.

8. The X-ray may give valuable confirmatory evidence. A definite diagnosis of tuberculosis is not justified on X-ray examination alone. In every case the interpretation of the X-ray plate should be made by one qualified to decide in such matters.

9. In all cases in which there is doubt, it is better to make a provisional diagnosis of tuberculosis and to give the child the benefit of hygienic measures and prolonged observation, although this need not necessarily mean that the child be sent to a sanatorium or hospital or be definitely stamped as a consumptive.

10. Finally, a correct diagnosis can be reached only by means of common sense and a careful consideration of a multiplicity of minor signs and symptoms, local and constitutional.

## THE DIAGNOSIS OF PULMONARY TUBERCULOSIS IN ADULTS WITH NEGATIVE SPUTUM

### *Definitions*

*1. Loss of weight.* By "loss of weight" should be understood an unexplained loss of at least 5 per cent below normal limits for that particular individual within four months time.

*2. Loss of strength.* By "loss of strength" in its pathological sense is meant undue fatigue and a lack of staying power which are unusual for the individual patient and which cannot be satisfactorily explained.

*3. Fever.* An occasional temperature of 99 should not be considered "fever." A temperature which persistently runs over 99.4 when taken at least four times a day over a period of one week (by mouth five minutes) should be considered of significance and to constitute "fever."

*4. Elevation of pulse.* Where the average normal pulse of the patient is already known, an elevation of 15 beats per minute when the pulse is taken quietly at home during various periods of the day should be considered abnormal. In cases where the average pulse is not known, and of course this constitutes the majority of cases, one should consider an average pulse of 85 or over in men and 90 or over in women to be abnormal. The combination of a subnormal temperature and an elevated pulse as defined here should be considered of great importance.

*5. Hemorrhage.* Any amount of expectorated blood, with or without sputum, may mean that tuberculosis is present and requires careful and thorough medical investigation as to its source. Blood streaks, blood spots, etc., may or may not mean tuberculosis. On the other hand a hemorrhage of one or two teaspoonsful is presumptive evidence of the disease.

*6. Family history.* An occasional case of tuberculosis in the patient's uncles, aunts, cousins, etc. should not be considered of importance, unless there has been intimate exposure and personal contact with such a case. It is an important fact when the patient's immediate relatives such as brothers, sisters, father, mother or grandparents have been tuberculous, and especially so, when there has been prolonged and intimate contact.

*7. Exposure.* Childhood exposure is of the greatest importance. Moderate exposure among normal, healthy adults of cleanly habits is of less importance. Of course, prolonged contact, with unhygienic habits or surroundings, may be a dangerous factor at any age.

*8. Cough.* There is no cough characteristic of tuberculosis. Every cough that persists for six weeks or over requires investigation. Tuberculosis may exist without any cough whatsoever.

*9. Sputum.* The presence of sputum is not necessary for a positive diagnosis. The constant raising of sputum, with or without cough, requires investigation. Absence of bacilli in the sputum after one or several laboratory examinations is not necessarily proof against the presence of active tuberculosis.

*10. Hoarseness.* Any hoarseness or a persistent "huskiness" requires investigation.

### *Minimum standards*

On a basis of these definitions the following minimum standards in the diagnosis of pulmonary tuberculosis have been formulated:

1. When constitutional signs and symptoms and definite past history are absent or nearly so, there should be demanded definite signs in the lungs, including persistent rales at one or both apices. By "persistent" it is meant that the rales must be present after cough at two or more examinations, the patient having been under observation at least one month.

2. In the presence of constitutional signs and symptoms such as loss of weight and strength, etc. as defined above, there should be demanded some abnormality in the lungs, but not necessarily rales.

3. Usually a process at the apices should be considered tuberculous and a process at the base to be non-tuberculous until the contrary is proved, excepting when a clear history of pleurisy is present.

4. A hemorrhage as defined above is evidence of active pulmonary tuberculosis until the contrary is proved.

5. One should consider a typical pleurisy with effusion as presumptive evidence of tuberculosis. One should also consider a dry pleurisy evidence of slight tuberculosis.

6. Pain in chest and shoulders, night sweats, digestive disorders, etc. may be present and should be investigated. Fistula in ano should be considered as a tuberculosis manifestation, requiring careful examination of the lungs for traces of the disease.

7. In every doubtful case one should demand that the patient be kept under observation for at least one month, with repeated sputum examinations, before a definite diagnosis is made.

## THE CLASSIFICATION OF PULMONARY TUBERCULOSIS

### *The National Association Classification (with modifications suggested by Dr. W. L. Rathbun of Otisville Sanatorium)*

The classification of pulmonary phthisis has always been of interest to the medical profession, particularly to those especially interested in tuberculosis. Numerous classifications have been suggested, including those of Trudeau (1887), Grancher (1890), Frankel (1902), King (1903), etc.

The National Association classification is considered an improvement upon any previous attempts and may be stated concisely as follows:

*Incipient.* Slight infiltration limited to the apex of one or both lungs or a small part of one lobe. No tuberculous complications.

Constitutional symptoms (including gastric or intestinal disturbance, or rapid loss of weight) may be slight or absent. There may be slight or no elevation of temperature or acceleration of pulse at any time during the 24 hours. The expectoration is usually small in amount or absent. Tubercle bacilii may be present or absent.

*Moderately advanced.* Marked infiltration more extensive than under incipient, with little or no evidence of cavity formation. No serious tuberculous complications and no marked impairment of function, either local or constitutional.

*Far advanced.* Extensive localized infiltration or consolidation in one or more lobes, or disseminated areas of cavity formation. Serious tuberculous complications, with marked impairment of function, local or constitutional.

*Acute miliary tuberculosis.* In this classification, each of the three stages is based on certain specific pathological findings and clinical symptoms. Unfortunately, however, lesions and symptoms are not interchangeable, but are immobilized in each of the three stages. This is confusing, for occasionally an advanced case may present only incipient symptoms, or vice versa.

Consequently, Dr. Rathbun has suggested the listing of lesions and symptoms under separate headings, thereby making it possible to classify any case in accordance with the exact extent of pulmonary involvement and nature of symptoms.

Rathbun's suggested arrangement, adopted by the American Sanatorium Association in December, 1916, is as follows:

| *Lesions* | *Symptoms* |
|---|---|
| *Incipient.* Slight infiltration limited to the apex of one or both lungs, or a small part of one lobe. No tuberculous complications. | A. (Slight or None) Slight or no constitutional symptoms, including particularly gastric or intestinal disturbance, or rapid loss of weight; slight or no elevation of temperature or acceleration of pulse at any time during the 24 hours. Expectoration usually small in amount or absent. Tubercle bacilli may be present or absent. |
| *Moderately advanced.* Marked infiltration, more extensive than under incipient, with little or no evidence of cavity formation. No serious tuberculous complications. | B. (Moderate) No marked impairment of function, either local or constitutional. |
| *Far advanced.* Extensive localized infiltration or consolidation in one or more lobes. Or disseminated areas of cavity formation. Or serious tuberculous complications. | C. (Severe) Marked impairment of function, local and constitutional. |

This scheme offers definite arrangements, making feasible the exact labelling of any individual case. The following combinations are possible:

| | | |
|---|---|---|
| Incipient A. | Moderately Advanced A. | Far Advanced A. |
| Incipient B. | Moderately Advanced B. | Far Advanced B. |
| Incipient C. | Moderately Advanced C. | Far Advanced C. |

For instance, "Incipient A" means an individual with an incipient lesion and with symptoms characteristic of the incipient stage, as defined above.

"Far Advanced A," however, means an individual with a far advanced lesion, but with only incipient symptoms—a combination not infrequently met with.

It would seem that the above arrangement is an improvement upon the National Association classification, and in view of the importance of the scientific aspects of the tuberculosis work being carried on, it is hoped that the above suggestions, subject of course to modification by local medical opinion, may be studied and utilized in the classification of Pulmonary Tuberculosis in Framingham.

## STANDARDS OF TREATMENT FOR PULMONARY TUBERCULOSIS IN ADULTS

Adult consumptive patients may be divided into three groups as far as treatment is concerned.

1. Suspicious cases, cases under observation, and those in whom the diagnosis is not absolutely definite.

2. Cases in whom the diagnosis is definite and in whom the disease is active.

3. Arrested and apparently arrested cases, discharged sanatorium cases, and those in whom the disease is inactive.

*1. Suspicious cases,* etc. The majority of this group can be treated at home until they fall into Group 2 or 3. It should be made clear in every instance that the patient is on trial and that more radical measures, such as going to a sanatorium or elsewhere, may be and very likely will be necessary. In a few cases of this group, sanatorium or hospital treatment, if it can be obtained *at once,* is of great value educationally and otherwise and entirely justified in order to clear up a diagnosis in instances where adequate home treatment is not possible.

*2. Cases in which the diagnosis is positive,* with or without a positive sputum. Sanatorium or hospital treatment *at once,* and to be continued

as long as the physician considers it necessary, is the ideal to be sought for *in the great majority of cases.* Home treatment may be substituted:

(a) When there are no children in the family who might be exposed to the disease in the open form.

(b) When the intelligence of the patient or the patient's family is such that adequate carrying out of details is possible.

(c) When adequate nursing and medical supervision is available over a sufficiently long period of time.

(d) When there are facilities at home for proper outdoor treatment under favorable hygienic surroundings.

*3. Arrested and apparently arrested cases,* discharged sanatorium cases, and those in whom the disease is inactive. Close medical and nursing supervision is essential in these cases, if the good done at the sanatorium is to be made permanent. There is no class of patients in whom hard work on the part of the physician and nurse will bring about better returns. Home treatment is naturally the best for the majority of these cases. How strict this should be in regard to outdoor sleeping, rest, etc., depends on the individual case. Frequent visits to the home by the nurse, and monthly examinations at the dispensary or doctor's office should be required. The amount of work done, and the choice of employment, are to be decided by the physician.

It should be explained to the patient that it may become necessary at any time for him to return to the sanatorium or hospital on signs of an impending breakdown.

Common sense, optimism, patience and tact, are essential factors in treatment.

# MEDICAL NOTES, ABSTRACTS AND REVIEWS

**It will be the eventual purpose of the REVIEW thoroughly to canvass all literature on tuberculosis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Abstract Editor, Dr. George Mannheimer, 41 West 51st Street, New York, N. Y.**

**Isolation and Treatment of Tuberculous Soldiers at Paris.**—Mesureur is chief of the entire public hospital system at Paris, the *Assistance Publique*. He here reports what has been accomplished since the municipal authorities in March, 1916, appropriated over $1,000,000 to erect barracks for tuberculous soldiers. By May, 1917, ten pavilions were in operation, with accommodations for 700 men. They were erected on the grounds of nine Paris hospitals, including the Laennec and the Salpétrière. Other pavilions with a total capacity of 1400 beds are being constructed on the grounds of four large hospitals in the suburbs. Some of the pavilions, such as the one at the Tenon Hospital, have been constructed of reënforced concrete. For a capacity of 600 beds this costs per bed only 2500 francs instead of the 7500 francs required for stone, brick and iron ($500 instead of $1500). The soldiers are distributed in the pavilions according as they are taking sanatorium treatment or are convalescing or in advanced stages of the disease. There are numerous advantages in thus having the tuberculous soldiers within close reach of their families, either in the city or suburbs.—*L'isolement et le traitement des militaires réformes tuberculeux à Paris, Mesureur, Bull. de l'Acad. de. M., June 12, 1917, lxxviii, no. 24.*

**The Diagnosis of Tuberculosis in Recruits.**—In view of the approaching assembling of the new armies under the draft, it becomes urgently necessary to consider the irreparable loss to the nation brought about by the undue proportion of tuberculosis in the classes which will come up for national service. Among the masses of humanity from which selection will be made, there is a fixed number who have, or have had, pulmonary tuberculosis, and the problem for the examining surgeon is how to judge wisely and not include in the draft any individuals who could possibly be the subjects of latent infection. Diagnosis, often a most difficult matter in civil life, has evidently gathered new difficulties in the case of soldiers. For example, the known facts of tuberculosis—that infection, latent or acute, exists in most adults, that immunity is acquired, and that the number of non-fatal lesions increases with age—are somewhat difficult to reconcile with the rule of the army medical examination. Thus in England, stirred by the experience of France, the recruiting boards are forbidden to take into the army men "who have been under treatment in a sanatorium, and men who have been notified as suffering from tuberculosis." That the first should be rejected is clearly right, although ex-sanatorium patients have found their way into the army and have done good work; but it is asked, especially by French physicians, whether the rejection of all the notified men is quite consistent with the idea that tuberculosis is so universal as alleged, and that it is often healed or cured. It seems evident that, if physicians are prepared to accept the doctrine that 95 per cent of adults have been infected, army examiners ought, in consistency, to accept the "healed" and even the "arrested" cases. Nevertheless, in England the rule rejecting them is rigid, but French opinion appears to justify the acceptance of the "healed" cases, if by "healed" be meant a cicatrized lesion, and not one that is continually passing into active tuberculosis.

There is another form of rejection which, in France, is regarded as seriously faulty in respect to diagnosis. We mean those cases classified as "suspicious," or rather, as tuberculous "suspects." According to Sergent, the diagnosis "suspected" tuberculosis indicates a small amount of concrete knowledge. Upon examination, most of these men turn out to be healthy or instances of pleurisy, bronchitis, trench coryza, dyspepsia, mitral stenosis, simple fatigue of body and mind, with a few that are simply shamming. Examples of such diagnostic errors, resulting from a wrong interpretation of x-ray plates and physical signs, are so common in the records of the army clearing

stations, or *centres de triage*, that some examiners, like Rist, propose a sole criterion of tuberculosis and, therefore, a sole cause of rejection, and that is the tubercle bacillus in the sputum. This is too rigorous, and also throws open the door too wide; for the bacillus may not be found, and, on the other hand, there are physical signs which are sufficient. The most trustworthy, Sergent believes, are the following: dulness, hemoptysis, increased fremitus, "clicks," and a veil or shadow at the apices, fixed, not modified by cough, with striae and fly spots on the plate. These are evidences of a lesion of the parenchyma of the lungs. A pleural lesion shows the same veil or shadow, but it is movable; there is inequality of the pupil on the affected side, with friction sounds, and increased vocal fremitus, tracheobronchial adenopathy, and, curiously enough, tubular breathing, which in these cases is not a sign of pulmonary cavity, but of nasal obstruction. The x-ray pictures are telescopic; they show cavities not discovered by the most careful auscultation, but they do not enable us to ascertain whether a lesion is active or latent, whether it is pleural or parenchymatous, whether the disease is in a stage of evolution or of decline. Unfortunately this is a question of primary importance to the army surgeon.

The proportion of veils or apical shadows on radioscopy and on the x-ray plates was 63 per cent. Apparently they are signs of healed lesions or of pleurisy of the apex. It is a significant fact that most of the recruits were rejected on this evidence; when reëxamined by experts at the *centres de triage* they were sent to the colors. This particular error is chiefly the work of examiners, who look at the men through the spectacles of the tuberculophobe. His tendency to see tuberculosis in every abnormal respiratory sign is a fallacy which may take root here. Many of the classical signs—harsh and rough breathing, weak breathing, and bronchophony—have the misfortune, shared by most constitutional signs—anemia, cough, fever and weakness——of being somewhat equivocal. The evil may be overcome by careful preliminary definition and history-taking, but the man of routine, without time for individual selection, does not supply these things, and the original application of the words to a particular phase of bronchial disorder seems to have clung about them with a misleading effect. The result is that great numbers of sound men are rejected, and two classes of bugbears have arisen,—the true and the false tuberculous. As is usual with definitions and classifications, however, this distinction between true and false cases does not exactly represent the actual fact. True and false tuberculosis overlap and blend into each other. The diagnosis in all these cases is very difficult. It is a question how it is to be done without national loss through mistakes.—*Editorial, Boston M. & S. J., Aug. 2, 1917, clxxvii, no. 5, 160.*

**Variations in Pulmonary Voice Sounds.**—One hundred cases were examined with the object of determining the variations to be found in chests which might be classed as normal. All abnormal cases were excluded, as well as those with a history of pneumonia, pleurisy, etc. Ninety-eight were women and two men Three patients were submitted to x-ray examinations for confirmation of the term "normal" and failed to show cause for variations in physical signs. The method of comparison was used. The conclusions reached are as follows:

Spoken voice is audible over the whole chest, whispered voice often only above the clavicle and spine of scapula. The transmission of the spoken and whispered voice over normal chests presents considerable variations. These variations do not follow with any degree of accuracy those in pulmonary resonance save over the right apex. The spoken and whispered voice are most often louder over the right apex, front and back, and generally so, also, over the left base.—*Variations in Pulmonary Voice Sounds. W. D. Reid, Boston M. & S. J., April 26, 1917, clxxvi, no. 17, 601.*

**Inspection in Pulmonary Tuberculosis.**—Inspection in tuberculosis should begin with the entrance of the patient into the office. Everything about him, as gait, facial expression, posture, etc., should be carefully noted. While standing or while seated the patient may try in various ways to fix the diseased side or to give more room for expansion of the sound side.

The patient should undress in the presence of the physician, who notes the various movements assumed by him. On close examination it will be noted that the hair is dry, lusterless, and faded in color. Almost invariably dandruff is present. Evidence of faulty nutrition will be found together with blemishes. The eyes early in the disease are lustrous, later they are dull and sad looking. The sclerae are pale. The lips may be parched, slightly cyanotic or anemic.

In inspecting the chest note the different shades on the chest walls, suspecting the deeper shades; note spastic muscles in the neck; a thickened sterno-mastoid is suggestive. The clavicle is more prominent on the affected side, the outer third is flatter

and the curved inner part more curved. The clavicular fossae are deeper on the diseased side. There is diminished respiratory expansion on the bad side. Sighing and frequent deep breaths should arouse suspicion.

It should be emphasized that each sign by itself is of no special weight, but a number of them together are significant in the diagnosis of tuberculosis.—*Observation and Inspection in the Physical Examination in Pulmonary Tuberculosis. C. Rawevsky, N. York M. J., July 14, 1917, cvi, no. 2, 66.*

**Differential Diagnosis in Pulmonary Disease.**—Correct diagnosis of early pulmonary tuberculosis is now made much more frequently than heretofore. Much less harm is done in stamping a dubious case as tuberculous than when an actual case of tuberculosis is overlooked. But excess of care in the making of a diagnosis may now and then lead to error. The following is a summary of symptom-complexes in which other explanations present themselves rendering a diagnosis of tuberculosis unnecessary.

(1) Tuberculous infection versus tuberculous disease: The presence of physical signs alone shows the presence of an inactive lesion, and no diagnosis of active tuberculosis should be made unless clinical symptoms are associated. The x-ray is of great aid in these cases. (2) Disturbances of internal secretions with neuroses: These cases have definite symptoms resembling those of tuberculosis, but physical signs are absent. Generally these are cases of hyperthyroidism and neurasthenia. (3) Bronchiectasis: Lesion in these cases is almost always in the lower lobes, and may be associated with or dependent upon a tuberculous lesion. If the bronchiectasis is single, the diagnosis may not be difficult, and is based on the localization of physical signs over the lower lobe behind, the absence of tubercle bacilli in the sputum, the history and the x-ray. With multiple or bilateral lesions, the diagnosis is more difficult. In all types the x-ray furnishes the most definite aid in the diagnosis. (4) Subacute and chronic non-tuberculous pulmonary infection: The clinical story in these cases is somewhat as follows: Mild illness, fever and cough. The diagnosis of grippe and bronchitis is usually made. The consitutional symptoms subside, leaving the cough and expectoration with or without hemoptysis. Physical examination shows a lesion in the lower lobe, the signs being those of an infiltration. The sputum is negative for tubercle bacilli but shows pneumococci, influenza bacilli, or streptococci. X-ray shows either nothing or simply an intensification of the bronchial shadows quite different from a tuberculous lesion. The majority of cases clear up. It is to be differentiated from tuberculosis by its constant localization in a lower lobe, by the absence of constitutional symptoms in the presence of extensive physical signs, by the absence of tubercle bacilli and the presence of organisms of acute respiratory disease and by the disappearance of signs and symptoms more quickly than would be possible in tuberculous lesions of similar extent.—*Some Problems of Differential Diagnosis in Chronic Pulmonary Disease. J. A. Miller, N. York M. J., April, 28, 1917, cv, no. 17, 773.*

**Coördinating Methods in Diagnosis of Tuberculosis.**—Laboratory methods have their value in the diagnosis of tuberculosis but too much must not be expected of them and in our efforts to recognize early cases the old hard route of physical diagnosis, history and clinical study, is the main one to be relied upon. Tubercle bacilli are not present in the sputum in early, closed, tuberculosis and even in open cases a number of specimens may have to be examined before their presence can be demonstrated. In fibroid phthisis the bacilli lose their acid-fast properties and will not stain. In such cases the Much granules should be looked for. In the examination of the sputum search should also be made for other organisms which may give rise to conditions simulating tuberculosis, e.g., the influenza bacillus, which often produces a chronic bronchitis; the aspergillus, which produces a picture resembling pulmonary tuberculosis; leptothrix bacilli, which are acid-fast and produce lesions which often resemble those produced by the tubercle bacillus. The limitations of the various tuberculin tests are well known. The value of the complement-fixation test has not yet been established. The x-ray fails to reveal the catarrhal bronchitis or the pulmonary infiltrations which constitute the progressive territory of the disease. Its value in early tuberculosis does not equal the older if less fashionable clinical methods. Certainly the Roentgen ray seldom warrants the diagnosis of a tuberculous process, without the support of clinical evidence obtained by careful study of the history of the case, and a physical examination.—*The Necessity of Coördinating Methods in the Definitive Diagnosis of Pulmonary Tubercular Lesions. F. B. Wynn, J. Ind. State M. Ass., January 15, 1917, x, no. 1, 15.*

**Detection of Early Tuberculosis.**—To make an intelligent search for early

pulmonary tuberculosis it is necessary to keep in mind the pathology of the tubercle. A careful history is indispensable. It must include a history of any possible exposure in childhood, whether breast-fed, number in family, number of wage earners, quality and quantity of food, number and size of rooms, ventilation, and any illness of childhood. Occupation, environment and number of working hours, as well as personal habits when off duty with special reference to the use of alcohol must also be considered. It is important to ascertain when the patient was last well.

A record of one week's temperature taken every two hours, a record of the weight, a table of standard weights according to height and some means of measuring the height are necessary.

The records of the Cook County Tuberculosis Hospital for cases defined as incipient show that the most common first symptoms were in order of frequency: cough, loss of appetite, pleurisy, loss of weight and blood-spitting. Loss of appetite and strength were the most common early symptoms in those cases which gave more than one symptom. The location of the disease was most commonly in the right apex, then left apex, right and left apices, and right hilus, in the order given. In 96 incipient cases the sputum was positive for tubercle bacilli in 47 cases in the following order: First examination, 27; second, 10; third, 3; fourth, 4; sixth, 2; and eighth, 1. The greatest number of negative examinations in any one case was fifteen. The use of tuberculin for diagnostic purposes is potent of much harm. An x-ray examination, if made by an expert, is a valuable adjunct.—*The Detection of Early Pulmonary Tuberculosis. E. Morris, Kentucky M. J., March 1, 1917.*

**Early Diagnosis.**—The diagnosis of early pulmonary tuberculosis belongs to the general practitioner. Only active tuberculosis concerns the clinician and the patient. The diagnosis is often difficult, and frequently impossible to make immediately. In suspicious cases the diagnosis should be worked out by all means available.

The chief symptoms, among which are epigastric pain, palpitation, flushing of the face, fatigue, etc., are often suggestive of something remote from the seat of pathology. A history of a previous pleurisy, especially with effusion, a local focus in the tonsils or glands, hemoptysis, or exposure is of great significance.

The examination consists of two parts, physical and laboratory. The former includes a study of the temperature chart, weight chart under forced feeding, and repeated chest examinations for a period of ten days, the patient continuing his occupation meanwhile. Persistent slight temperature rise, with an increased pulse, stationary weight, and the presence of râles, particularly the latent râle, spell presumptively early tuberculosis.

The laboratory examination comprises the sputum, skin, blood, x-ray, and the complement fixation tests. The sputum if negative is not conclusive. The blood count is of little significance. The x-ray and fluoroscope are of little value in determining early pathologic activity. The complement fixation test is not only of value in the diagnosis, but it also shows as long as it is positive that cases considered cured are not entirely free from infection.—*Diagnosis of Early Pulmonary Tuberculosis. J. I. Johnston, Am. J. M. Sci., July, 1917, cliv, no. 1, 100.*

**X-Ray Diagnosis in Chest Diseases.**—The x-ray is of recognized value in the diagnosis of diseases of the chest. Of course the plates must be properly made and interpreted. Pulmonary tuberculosis: Can be recognized as early as there are tissue changes which will produce some variation in the density of the lung. Minute tubercles are seen most frequently at the apices. In children the disease extends outward from the roots of the lungs. In early tuberculosis the disease is seen in the distribution of the terminal bronchi. Consolidation and cavitation can be clearly detected on the plate. Extension of the disease downward suggests tuberculosis. The diseases most difficult to differentiate from early tuberculosis are metastatic carcinoma, leukemia, and syphilis. Metastatic carcinoma: Generally this disease spreads outward from the roots of the lungs or from the mediastinum. The disease develops from some point and invades surrounding tissue by direct extension, presenting, a more uniform appearance than tuberculosis. Rarely if ever are there cavities. Leukemia: Presents a general mottling similar to tuberculosis, but is more apt to be a general affection. Syphilis: Is rare. Involvement of the lung is more apt to be of a general character, or to extend outward from the roots. Bronchiactasis: This disease affects the bases of the lungs most often, and above the lower bronchial trees. Broncho-pneumonia. In most cases the disease extends outward from the roots. Lobar pneumonia: Usually occupies one of the lobes. Tumors of lungs: Are practically all secondary, therefore the history will differentiate. Metastatic Sarcoma. Is secondary, and presents sharply

defined nodules scattered through the lungs. Acute pleurisy. Cannot be diagnosed by x-ray, with the exception of showing the limited motion of the affected side. Chronic pleurisy: Is generally associated with adhesions, and therefore shows, when it involves the diaphragm, interference with its movement. If the pleura is greatly thickened it will give some decrease in transparency. If it is tuberculous there is frequently associated tuberculosis of the lungs. In effusion an upper level of increased opacity is observed, the line being curved outward and upward. The character of the fluid is rarely differentiated by x-rays. In a general way empyema gives a slightly greater increase in density. Encysted pleural effusion or encapsulated empyema: Present a dense area surrounded by clear lung tissue, the lines being sharply defined. Abscess: Early presents a localized consolidation, shading gradually into the surrounding tissue; later gives a cavity surrounded by consolidation progressively shading into the surrounding tissue. If it is tuberculous, other evidence of tuberculosis will be present; if pyogenic it is likely to occupy the central part or the base of the lung. Gangrene: Presents the same picture as abscess.

In the study of the heart observe the size, position, shape, and the contractions. The size and position vary normally, but the shape is of great diagnostic value. In hypertrophy of the left ventricle there is a distinct projection to the left and a distinct enlargement of the left ventricle. In general dilatation the heart changes from the pear shape to a globular form. The contractions are perhaps of greater value than the shape. In general dilatation they are rapid, flabby and more or less wavy. Pericardial effusion: There is a triangular sac, with the base at the bottom.

The great vessels are important for observation. General or local atheroma is early recognized. Aneurysms present expansile pulsation, the tumor being along the aorta. Mediastinal tumors have no expansile pulsation.—*X-Ray Diagnosis in Disease of the Chest. G. E. Pfahler, N. York M. J., July 14, 1917, cvi, no. 2, 53.*

**X-Ray Diagnosis in Pulmonary Tuberculosis.**—The Roentgen ray will often give us our first definite knowledge of the existence of tuberculosis. It will show central and deep lesions where other methods fail. It will also show the presence of mediastinal lesions where percussion and auscultation have failed. The Roentgen ray findings are of great value in prognosis, since by means of the x-ray plate we can discover the presence of cavity and involvement of the bases, which speak for a bad prognosis. The x-ray will often show an advanced stage where the physical signs pointed to an early process.—*The Roentgen Ray Diagnosis in Pulmonary Tuberculosis. R. C. Beeler, J. Ind. State M. Ass., January 15, 1917, x, no. 1, 18.*

**X-Ray Diagnosis.**—Roentgenology offers more conclusive evidence, either positive or negative, upon the question of early pulmonary tuberculosis than any other single procedure. The tuberculin test, properly administered and interpreted, comes second; physical signs third; and history fourth. The latter is chiefly valuable when it shows exposure to infection. The onset of the disease and the history of subjective symptoms are not unlike those of any other low-grade chronic infectious process. The pathognomonic x-ray signs of pulmonary tuberculosis are a soft, indistinct mottling at the periphery of the upper lobe, with pinpoint to pinhead sized shadows, and a fine cobweb like network of linear shadows which is especially characteristic when it occurs in that part of the lung field where markings of any description are normally absent. In most cases one is able to trace a direct connection between these shadows and similar ones at the hilus of the lung. Differential diagnosis must include anthracosis, chronic passive congestion, streptococcicosis, syphilis and bronchiectasis. The roentgenologist of today is coming to believe that many transitory or non-lethal lung infections have hitherto passed unrecognized, because of their failure to supply autopsy material for study. Roentgenology is arousing a clearer, if not a new, conception of the variety of clinical types of pulmonary tuberculosis. A logical prognosis may, even at an early stage of the disease, be based in part upon data furnished by the Roentgen examination.—*The Diagnosis of Concealed Pulmonary Lesions with Special Reference to Tuberculosis. F. S. Bissell, St. Paul, M. J., April, 1917 xix, no. 4, 112.*

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* "The Choice of Tuberculins," by Benjamin White, Otisville, N. Y., Department of Health, City of New York. Read at the annual meeting of the Medical Society of the State of New York, at Saratoga Springs, May 18, 1916.

† Human or bovine type.

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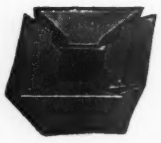

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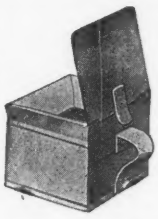

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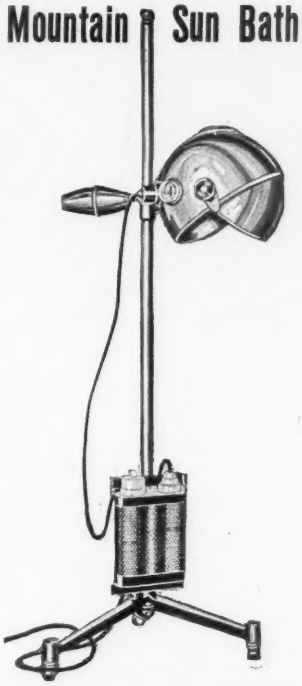

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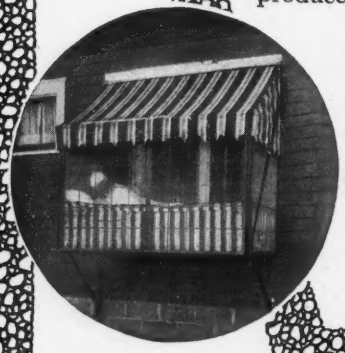

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